Archives of Internal Medicine

VOLUME 55 APRIL 1935 NUMBER 4

CARDIAC OUTPUT AND RELATED FUNCTIONS UNDER BASAL AND POSTPRANDIAL CONDITIONS

A CLINICAL STUDY

SIDNEY A. GLADSTONE, M.D.*

NEW YORK

Since the function of the heart is to pump into the arteries the blood received from the veins, there is perhaps no more pertinent question regarding cardiac action than the amount of blood which the heart pumps during a given time. That amount is usually designated as the minute volume or cardiac output and is conveniently expressed in liters per minute. In the normal adult of average size under basal conditions the cardiac output is about 4 liters per minute. This applies to either ventricle, since the output is the same for both sides. With a pulse rate of 70 per minute, the systolic output averages 60 cc., or about 2 ounces.

The intimate relation of the digestive and circulatory systems is indicated by the influence of digestion on the pulse rate, blood pressure, circulation time and cardiac output. The pulse rate [1] and the systolic blood pressure are found to increase after eating, while the diastolic pressure may show a slight decrease.[2] The circulation time of the blood in dogs was studied by Sheard, McCracken and Essex [3] by injecting radium C into the jugular vein and measuring the time which elapsed before its arrival in the femoral artery, as detected by a radiosensitive electroscope. "The results of the investigation show that the circulation time of the blood in dogs previously fasted is reduced 20 to 35 per cent during the digestion of a mixed meal." It should be noted that a determination of the circulation time gives the time consumed by the fastest moving particles in the blood stream while traveling from one arbitrarily chosen point to another. This may or may not be a

* Richard and Ella Hunt Sutro Fellow for Cardiovascular Research.

From the medical service of the Mount Sinai Hospital.

1. Rihl, J.: Die Frequenz des Herzschlages, in Bethe, A.; von Bergmann, G.; Emden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1926, vol. 7, p. 449.

2. Janeway, T. C.: The Clinical Study of Blood Pressure, New York, D. Appleton and Company, 1904.

3. Sheard, C.; McCracken, E. C., and Essex, H. E.: The Circulation Time of the Blood in Dogs Before and During the Digestion of Food, Am. J. Physiol. **109**:96, 1934.

linear function of the average rate of flow. Although it gives no quantitative idea of the amount of blood circulating through the vessels or even of the average rate of flow (since the velocity in the center of the stream is greater than that at the periphery), it is useful in detecting relative changes.

Herrick and her associates [4] applied the thermostromuhr method of Rein to study the effect of digestion on the rate of flow in the femoral, carotid and mesenteric arteries and the external jugular vein. These authors stated:

> . . . contrary to current belief we have found that blood is not diverted from the somatic tissue to the visceral organs during the digestion of food. Instead of a decrease in blood flow in the femoral and carotid arteries and jugular vein, there is a marked prolonged increase during the digestive cycle. This is likewise true in the mesenteric artery.

They found that during the third hour after digestion starts the blood flow in the femoral artery may be double the basal value. This doubling of the blood flow seems inordinately large as compared with the results of other workers as well as with the subsequent findings of Herrick and her collaborators,[5] who studied the effect of digestion of food on the liver of the dog and reported an average increase in the blood flow of about 54 per cent.

DIGESTION AND CARDIAC OUTPUT

In man, the effect of digestion on the cardiac output was studied in one subject by Jarisch and Liljestrand,[6] in six by Kisch and Schwarz [7] and in six by Grollman.[8] All these workers found an increase in the cardiac output. Grollman, who made the most extensive study, reported that "the cardiac output rises immediately after the ingestion of food, reached a maximum of 0.5 to 2.0 liters over the fasting level, and remains at this high and practically constant level for one to three hours."

These studies of the effect of digestion on the circulation in the dog and in normal man have been sufficiently illuminating to warrant

4. Herrick, J. F.; Essex, H. E.; Mann, F. C., and Boldes, E. J.: The Effect of Digestion on the Blood Flow in Certain Blood Vessels of the Dog, Am. J. Physiol. **108**:621, 1934.

5. Herrick, J. F.; Mann, F. C.; Essex, H. E., and Boldes, E. J.: The Effect of the Digestion of Food on the Blood Flow from the Liver of the Dog, Am. J. Physiol. **109**:52, 1934.

6. Jarisch, A., and Liljestrand, G.: Ueber das Verhalten des Kreislaufes bei Muskelarbeit, nach dem Essen, und bei Flüssigkeitszufuhr, Skandinav. Arch. f. Physiol. **51**:235, 1927.

7. Kisch, B., and Schwarz, H.: Das Herzschlagvolumen und die Methodik seiner Bestimmung, Ergebn. d. inn. Med. u. Kinderh. **27**:169, 1925.

8. Grollman, A.: The Effect of the Ingestion of Food on the Cardiac Output, Pulse Rate, Blood Pressure, and Oxygen Consumption of Man, Am. J. Physiol. **89**:366, 1929.

their extension to an investigation of patients having some circulatory abnormality. I report, therefore, the results of forty-four determinations of the cardiac output and related functions made under basal and postprandial conditions in twelve subjects, five of whom had normal cardiovascular systems, while seven presented some structural or functional abnormality. In determining the cardiac output I used the acetylene method as described by Grollman.[9]

The question of the technic of the clinical determination of the cardiac output has stimulated a tremendous amount of effort, which is doubtless justified by its importance and is described in a voluminous literature. A short historical statement is offered to assist in the comprehension and critical evaluation of the method used in this study. During the past sixty years the problem of determining the cardiac output in man has been attacked in several ways. The first method was the attempt to estimate the cardiac output in man by making direct measurements on experimental animals and assuming the existence of some ratio based on the size of the heart and ventricles in man as compared with those of the animals studied.[10] These methods have no special clinical interest, but one is surprised to learn how well these indirect results compare with the later findings.

The second method is based on the important fact pointed out by Fick,[11] in 1870, and often called the Fick principle. If one measures the concentration of carbon dioxide or oxygen in the venous and arterial blood, one can determine the volume of oxygen taken up by each liter of blood as it passes through the lungs, as well as the volume of carbon dioxide given off. One can then, by means of a spirometer, determine the total volume of carbon dioxide given off or the total volume of oxygen consumed during one minute and can calculate the number of liters of blood that must have passed through the lungs to account for the liberation of the observed amount of carbon dioxide or the consumption of the observed amount of oxygen. In making this determination the arterial blood may be obtained from one of the peripheral arteries, such as the brachial, while the venous blood must be obtained from the right side of the heart, because only here does one obtain an aliquot sample of mixed venous blood; the gaseous content of specimens of venous blood obtained from peripheral veins varies with the metabolic activity of the local area drained. This method of determining the cardiac output is so direct and so reliable that it has

9. Grollman, A.: The Cardiac Output of Man in Health and Disease, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

10. Tigerstedt, R.: Die Geschwindigkeit des Blutes in den Arterien, Ergebn. d. Physiol. **4**:481, 1905.

11. Fick, A.: Ueber die Messung des Blutquantums in den Herzventrikeln, Sitzungsb. d. phys.-med. Gesellsch. zu Wurzburg, 1870, p. 16.

been used as a basis of comparison for testing the validity of other, less direct, methods. The objection to cardiac puncture has restricted the use of the method to experiments on animals. Recently, however, Baumann [12] and his co-workers applied the method to man and provided the means of testing the many indirect methods that have been used in determining the cardiac output in man. In order to avoid the necessity of arterial and cardiac punctures, many indirect breathing methods for obtaining the carbon dioxide concentration in arterial and venous blood have been suggested, but these methods have usually yielded inconsistent results and have proved inferior to the use of the foreign gas method, which is the third method that I shall consider.[9]

The foreign gas method was first attempted by Bornstein,[13] in 1910, when nitrogen was used without much success. The use of nitrogen monoxide was suggested the following year by Markoff, Müller and Zuntz.[14] This gas was then used by Krogh and Lindhard; [15] their method was modified by Marshall and Grollman,[16] who used ethylene as the foreign gas, until after further studies Grollman [17] found acetylene to be superior. A description of this method will suffice to illustrate the principles on which most of the foreign gas methods are founded.

The patient whose cardiac output is to be determined is permitted to breathe into and out of a 3 liter rubber breathing-bag containing a mixture of air and acetylene. The nose is compressed with a clip so that the lungs and bag form a closed system. After fifteen seconds of rebreathing to insure complete mixture, a sample of gas is admitted to an evacuated sampling tube. The patient continues to breathe into and out of the bag, and after from six to eight seconds another sample of gas is taken. During the few seconds which elapse between the drawing of the samples the composition of the mixture of gases has changed. Oxygen and acetylene have been in part absorbed by the blood passing through the lungs, and carbon dioxide has been given off. The two samples of gas are then analyzed to determine the extent to which the various gases have changed in concentration.

The purpose of this rebreathing procedure is to determine the arteriovenous difference for oxygen. For example, if one finds that 1 liter of arterial blood contains 60 cc. more oxygen than 1 liter of venous blood, a liter of blood must

12. Baumann, H.: Ueber die wahre Grösse des Minutenvolumens, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **42**:247, 1930.

13. Bornstein, A.: Eine Methode zur vergleichenden Messung des Herzschlagvolumens beim Menschen, Arch. f. d. ges. Physiol. **132**:307, 1910.

14. Markoff, I.; Müller, F., and Zuntz, N.: Neue Methode zur Bestimmung der im menschlichen Körper umlaufenden Blutmenge, Ztschr. f. Balneol. **4**:373, 409 and 441, 1911.

15. Krogh, A., and Lindhard, J.: Measurements of the Blood Flow Through the Lungs of Man, Skandinav. Arch. f. Physiol. **27**:100, 1912.

16. Marshall, E. K., and Grollman, A.: A Method for the Determination of the Circulatory Minute Volume in Man, Am. J. Physiol. **86**:117, 1928.

17. Grollman, A.: The Determination of the Cardiac Output of Man by the Use of Acetylene, Am. J. Physiol. **88**:432, 1929.

take up 60 cc. of oxygen while it passes through the lungs. One then measures the oxygen consumption, and if it proves to be 240 cc. of oxygen per minute, it is apparent that $\frac{240}{60}$, or 4 liters, of blood is passing through the lungs in one minute. The cardiac output, therefore, is calculated from the oxygen consumption and the arteriovenous oxygen difference. The oxygen consumption may be measured by means of the spirometer used for the determination of the basal metabolism. The arteriovenous difference is calculated from the change in concentration of the gases found in the two samples. Why is a foreign gas, such as acetylene, used in determining the arteriovenous difference for oxygen? The arteriovenous difference is simply another expression for the amount of gas which a liter of blood takes up or gives off while passing through the lungs. A foreign gas like acteylene is used because venous blood coming to the lungs contains none of this gas, and the amount taken away depends merely on the solubility of that gas in the blood. The amount of gas taken up indicates the arteriovenous difference for acetylene. While the blood passing through the lungs is taking up acetylene, it is also taking up oxygen. If it takes up the same amount of oxygen as acetylene, the arteriovenous difference is the same for both. Usually the amounts of the two gases are different, but the arteriovenous oxygen difference can be calculated from the ratio of the amounts of the two gases absorbed. The determination must be finished within twenty-three seconds; otherwise, the blood laden with acetylene will make a complete circuit of the body and come back to the lungs. Such blood, containing acetylene, will not be able to absorb the requisite amount of gas from the alveolar spaces. It is apparent that the entire calculation is based on the change in concentration of the gases during the few seconds which elapse between the drawings of the samples. Since the change in concentration is small, any errors in the analysis of the gases will be proportionately large. An error of 0.03 per cent in this analysis may produce a 3 per cent error in the arteriovenous difference and the cardiac output.

In making my determinations I followed the technic as described by Grollman [9] but made a change in the method of analysis of the gases which lowers the arteriovenous difference and increases the result for the cardiac output approximately 3 per cent. The equation for the arteriovenous oxygen difference is as follows:

$$\text{Arteriovenous difference} = \frac{(\text{difference for oxygen})\ (\text{average for acetylene})\ (\text{B-48.1})\ (0.00974)}{\text{difference for acetylene}}$$

The arteriovenous oxygen difference is finally given in cubic centimeters of oxygen per liter of blood. In the numerator, the oxygen difference represents the difference in concentration of the oxygen in the two samples; the average for acetylene is the average concentration of acetylene in the two samples, and B is the barometric pressure. In the denominator, the acetylene difference is the difference in the concentration of the acetylene in the two samples. During the interval between the drawing of the samples the volume of oxygen plus the amount of acetylene absorbed exceeds the volume of carbon dioxide excreted by the blood, resulting in a net decrease in the volume of the lung-bag system. This tends to make the percentages of the gases in the second sample too high or those in the first sample too low for comparison. The necessary correction is made by increasing the values found in the first sample proportionately to the increase found in the percentage of nitrogen, which presumably takes no part in the transepithelial gaseous interchange. For the derivation of the equation just given, as well as of the principles and assumptions on which it is based, the reader is referred to Grollman's excellent monograph.[9]

The results of an analysis of a pair of samples is given, and the calculation for the arteriovenous difference is indicated:

	Sample 1	Sample 1 (Corrected)	Sample 2	Difference (Percentage)
Carbon dioxide	5.37	.....	5.98	
Acetylene	10.71	11.06	9.16	1.90
Oxygen	15.30	15.79	14.03	1.76
Nitrogen	68.62	.....	70.83	

$$\text{Arteriovenous difference} = \frac{(1.76)\ (9.94)\ (760\text{-}48.1)\ (0.00974)}{1.90} = 63.8$$

The percentage composition of the mixtures of gases is found by introducing a known amount of gas into the buret of a modified Haldane apparatus and measuring the volume of the gas which remains after the successive removal of carbon dioxide, acetylene and oxygen, in the order named. The final volume of gas consists of nitrogen. For removing carbon dioxide a 10 per cent solution of potassium hydroxide saturated with sodium chloride is used; for acetylene a solution of an alkaline cyanide, and for oxygen an alkaline solution of pyrogallol. Grollman stated that acetylene is slightly soluble in the solution of potassium hydroxide, which results in a slight absorption of acetylene during the removal of carbon dioxide. Since the difference for acetylene would not be effected if the small error were equal in both analyses, Grollman recommended that during the analysis of each sample the gas be forced into the carbon dioxide absorber an equal number of ("eight or more") times. "One thus avoids the solution of an unknown and different amount of acetylene in successive samples." [9]

Although during the removal of carbon dioxide there is not sufficient time for the establishment of acetylene equilibrium as between the solution of potassium hydroxide and the overlying mixture of gases, nevertheless the amount of acetylene dissolved depends on the time of exposure, the pressure within the absorbing chamber, the temperature of the environment and other factors. Even though all the other factors are kept constant, the two samples differ in their concentration of acetylene, with a resulting increase in the partial pressure of the acetylene of the first sample as compared with that of the second. This would lead to a greater solution of acetylene during the absorption of carbon dioxide in the first, as compared with the second, analysis. This can be demonstrated by repeating the absorption in the potassium hydroxide after the carbon dioxide is removed. A small amount of acetylene will be dissolved. This is the equivalent of making a blank determination to see how much acetylene is absorbed under the physical conditions of the analysis. I found that the amount of acetylene absorbed during ten exposures in potassium hydroxide is less during the second than during the first exposure and less during the third than the second, etc. It is safe to assume that the amount of acetylene absorbed during ten exposures in potassium hydroxide at most equals but does not exceed the amount absorbed in the previous exposure. In analyzing my samples, therefore, I forced the mixture of gases into potassium hydroxide ten times. This is sure to absorb all the carbon dioxide and a small amount of acetylene. After the reading is taken the remaining mixture of gases is again forced into potassium hydroxide ten times in the same way. In this procedure a small amount of acetylene is absorbed. The second absorption of acetylene is always greater in the first sample than in the second, because the partial pressure of acetylene is higher in the first. This disparity confirms the theoretical conclusion already expressed that the small amount of acetylene absorbed in the samples during the removal of carbon dioxide is different because of the different partial pressure of the gas. The error involved can be partly corrected by subtracting the volume of acetylene absorbed during the second ten exposures

from the volume of carbon dioxide plus acetylene absorbed during the first ten exposures. When this is done, the determination already described would yield the following results:

	Sample 1	Sample 1 (Corrected)	Sample 2	Difference (Percentage)
Carbon dioxide	5.16	.....	5.86	
Acetylene	10.92	11.27	9.28	1.99
Oxygen	15.30	15.79	14.03	1.76
Nitrogen	68.62	.....	70.83	

$$\text{Arteriovenous difference} = \frac{(1.76)\ (10.10)\ (760\text{-}48.1)\ (0.00974)}{1.99} = 61.9$$

The correction indicates that the average for acetylene should be 10.10 instead of 9.94 and the difference for acetylene should be 1.99 instead of 1.90 per cent. Since one factor is in the numerator and the other is in the denominator, the two errors offset each other partly but not entirely, as is seen in the final result.

It is interesting to note that in the nine cases reported by Baumann and Grollman,[18] who compared the results of the acetylene method with those of the Fick principle, using the direct puncture of the right ventricle, the results in five instances agree within 2 to 3 per cent, and that in four of these five cases there was the slightly lower cardiac output which the principles just stated would lead one to expect from the method of analysis originally described.

In a personal communication to me regarding the findings just described, Dr. Grollman stated that the error discussed is theoretically possible but in his studies did not exceed 1 per cent. I found that the acetylene is more soluble in 10 per cent potassium hydroxide (saturated with sodium chloride) than in a saturated solution of potassium hydroxide but that the high viscosity of the latter renders it less sensitive to slight changes in pressure and less suitable for measuring changes in volume. The amount of acetylene absorbed varies with the number of times the mixture of gases is forced into potassium hydroxide. The amount of acetylene absorbed by potassium hydroxide is also somewhat greater when the solutions are cold than when they are warm. Because of these variable factors which influence the size of the analytic error, I believe that in performing these analyses it is important, first, to realize that an error is possible and, second, to determine its size and correct it. The size of the error is indicated in any individual analysis by the simple corrective procedure here described.

In studying the effect of digestion on the cardiac output, in most cases, I acquainted the subject with the complete procedure by making a test on the day before the experiment in order that the rebreathing be properly performed and the peculiar taste as well as the innocuousness of the acetylene become familiar. On the following morning the cardiac

18. Baumann, H., and Grollman, A.: Ueber die theoretischen und praktischen Grundlagen und die klinische Zuverlässikgeit der Acetylen Methode zur Bestimmung des Minutenvolumens, Ztschr. f. klin. Med. **115**:41, 1930.

Data on Effect of Digestion on the Cardiac Output Under Basal and Postprandial Conditions

Determination	Date, 1934	Subject	Diagnosis	Age, Years	Sex	Height, Inches	Weight, Pounds	Condition During Test	Pulse Rate	Blood Pressure		Oxygen Consumption, Cc. per Minute	Relative Value of Oxygen Consumption	Arteriovenous Oxygen Difference, Cc. per Liter of Blood	Cardiac Output, Liters per Minute	Cardiac Index	Relative Value of Cardiac Output	Systolic Output, Cc.	$\frac{S-D}{\frac{1}{2}(S+D)}$	Ratio of Systolic Output	$\frac{S-D}{\frac{1}{2}(S+D)} \times PR$
										Systolic	Diastolic										
1	4/18	I. L.	Normal	22	M	69	149½	Basal	54	112	72	230	100	64.3	3.57	1.97	100	66	435	659	235
2	4/19	.....	.....	..	..	..	...	2 hr. post prandial	60	130	60	291	127	65.6	4.43	....	124	74	736	995	442
3	....	.....	.....	..	..	..	...	3 hr. post prandial	60	128	65	276	120	67.1	4.11	....	115	69	653	946	392
4	5/24	L. T.	Normal	25	M	71	165	Basal	58	105	70	213	100	53.7	3.97	2.02	100	69	400	580	232
5	....	.....	.....	..	..	..	...	Basal	52	100	70	220	103	50.1	4.39	....	...	84	353	426	184
6	5/23	.....	.....	..	..	..	...	2 hr. post prandial	60	110	65	270	127	53.6	5.04	....	127	84	514	612	308
7	....	.....	.....	..	..	..	...	4 hr. post prandial	55	105	75	248	117	50.1	4.96	....	125	90	333	370	183
8	4/20	W. S.	Normal	17	M	67	142	Basal	56	112	58	222	100	61.3	3.62	2.09	100	65	636	979	356
9	4/21	.....	.....	..	..	..	...	2 hr. post prandial	63	115	58	270	122	62.8	4.29	....	119	68	657	967	414
10	....	.....	.....	..	..	..	...	3 hr. post prandial	63	115	62	272	123	57.4	4.73	....	131	75	598	798	377
11	4/13	A. F.	Colitis	13	M	64	101	Basal	86	105	55	175	100	49.0	3.57	2.46	100	42	625	149	537
12	5/ 7	.....	.....	..	..	..	...	2 hr. post prandial	80	95	50	206	118	52.1	3.95	....	111	49	620	127	512
13	....	.....	.....	..	..	..	...	3 hr. post prandial	84	96	50	[206]	...	44.5	4.61	....	129	55	630	115	529
14	4/30	M. B.	Duodenal ulcer	34	M	68	132	Basal	72	108	70	208	101	59.7	3.49	2.05	100	48	427	889	307
15	....	.....	.....	..	..	..	...	Basal	72	110	68	205	100	52.1	3.94	....	...	55	472	858	340
16	5/ 1	.....	.....	..	..	..	...	2 hr. post prandial	80	110	60	280	135	54.7	5.12	....	147	64	588	920	470
17	....	.....	.....	..	..	..	...	3 hr. post prandial	72	110	62	221	108	51.0	4.33	....	124	60	559	932	403
18	6/ 1	A. N.	Exophthalmic goiter	43	M	69	131	Basal	82	125	60	307	100	52.0	5.92	....	100	72	702	976	576
19	....	.....	.....	..	..	..	...	1½ hr. post prandial	90	132	55	324	106	54.0	6.01	....	102	67	824	1,230	742
20	6/ 2	.....	.....	..	..	..	...	Basal	80	120	60	289	100	55.7	5.19	3.04	100	65	667	1,025	534
21	....	.....	.....	..	..	..	...	1 hr. post prandial	82	130	50	300	104	54.1	5.54	....	107	68	889	1,307	729
22	6/ 9	D. L.	Exophthalmic goiter	37	M	65	119	Basal	92	130	60	283	100	56.3	5.03	3.20	100	55	737	1,340	677
23	....	.....	.....	..	..	..	...	1 hr. post prandial	96	140	40	302	107	57.9	5.22	....	104	54	1,111	2,042	1,066
24	6/ 8	.....	.....	..	..	..	...	1½ hr. post prandial	96	135	30	312	110	55.1	5.66	....	112	59	1,290	2,183	1,238
25	....	.....	.....	..	..	..	...	5½ hr. post prandial	96	135	55	298	105	57.0	5.23	....	104	55	842	1,532	808
26	5/18	H. C.	Hypertension, angina pectoris, thyroidectomy, hypothyroidism	38	M	69	142	Basal	50	130	90	164	100	65.9	2.49	1.41	100	50	364	728	182
27				..	..	..	...	Basal	52	135	95	181	110	72.8	2.49	....	...	48	348	725	181
28	5/17			..	..	..	...	1½ hr. post prandial	55	150	90	195	119	57.1	3.42	....	137	62	500	806	275
29				..	..	..	...	2 hr. post prandial	..	...	..	192	117	62.5	3.06	...	123				
30	5/22	A. H.	Essential hypertension	51	M	66½	142	6 hr. post prandial	75	228	138	289	...	52.3	5.53	....	...	74	492	667	368
31				..	..	..	...	3 hr. post prandial	76	230	130	320	...	56.1	5.71	....	...	75	556	741	423
32	5/21	.....	.....	..	..	..	...	1 hr. post prandial	80	230	130	337	...	53.1	6.35	....	...	79	556	704	449
33	6/ 5	E. F.	Hypertension, coronary sclerosis	45	M	69	135	Basal	72	185	120	230	100	59.1	3.89	2.25	100	54	426	789	306
34				..	..	..	...	1 hr. post prandial	75	145	80	279	121	49.0	5.70	....	147	76	578	761	433
35	6/ 6	.....	.....	..	..	..	...	Basal	72	190	120	210	100	60.9	3.45	....	100	48	452	940	325
36	....	.....	.....	..	..	..	...	1 hr. post prandial	75	150	85	222	106	52.3	4.25	....	123	57	553	970	415
37	5/31	H. C.	Arteriosclerotic heart disease	62	M	69	140	Basal	62	90	60	197	100	58.1	3.39	1.94	100	55	400	728	248
38	5/29			..	..	..	...	6 hr. post prandial	66	100	68	202	102	64.1	3.15	....	...	48	381	793	251
39	....	.....	.....	..	..	..	...	1½ hr. post prandial	66	95	55	245	124	62.9	3.89	....	115	59	534	905	352
40	5/11	G. S.	Syphilitic aortitis, aortic insufficiency, rheumatic (?) mitral disease	34	M	65	124	Basal	58	100	40	191	100	60.8	3.14	1.96	100	54	857	1,588	497
41	5/14			..	..	..	...	Basal	58	100	45	191	100	59.3	3.22	....	...	55	759	1,380	440
42				..	..	..	...	Basal	59	110	45	205	107	65.4	3.14	....	....	53	839	1,583	495
43	5/15			..	..	..	...	2 hr. post prandial	60	110	40	226	118	64.2	3.52	....	112	59	933	1,580	560
44	....	.....	.....	..	..	..	...	3 hr. post prandial	60	118	45	223	117	65.0	3.43	....	109	57	896	1,572	538

output was determined under basal conditions. A rather full breakfast, consisting in most instances of fruit, cereal, two eggs, toast and coffee, was given. The test was then repeated from one to three hours after the meal. In some cases, as is indicated by the dates in the table, the tests carried out under basal conditions and those carried out under postprandial conditions were performed on successive or different days. All the patients studied were lying comfortably in bed. With only one or two exceptions, the subject was permitted to lie quietly in bed for a full hour or more before a test was performed, in order to insure complete physical rest. The blood pressure was determined by the auscultatory method [19] with the aid of a mercury manometer. If good checks were not obtained on successive readings, the determination was repeated.

The results are shown in the table. In summarizing these findings I shall mention the general results common to all or most of the subjects and then consider the peculiar individual variations or points of interest noted. During digestion, as compared with the fasting condition with the patient at rest, there is a slight increase in the pulse rate together with an increase in the systolic pressure and usually a less marked fall in the diastolic pressure, resulting in an increase in the pulse pressure. The oxygen consumption, as is well known, increases during digestion. The individual increments, as observed from one to three hours after eating, vary in the normal subject from 18 to 35 per cent and average 25 per cent above the values during fasting. In the abnormal subject the increments vary from 4 to 24 per cent, and the average increase is only 13 per cent. From one to three hours after eating the cardiac output in the normal subject increases by from 11 to 47 per cent above the value during fasting, with an average of 25 per cent. In the abnormal subject the increments vary by from 2 to 47 per cent, the average increase being 17 per cent. Five or six hours after eating the cardiac output approximates the value during fasting. The cardiac index designates the basal cardiac output per square meter of body surface and in normal persons equals 2.2 ± 0.3.[9] The systolic output, which is found by dividing the cardiac output by the pulse rate, increases during digestion because the cardiac output shows a greater relative increase than the pulse rate.

The extra demands made on the heart during digestion, especially after a large meal, give some clue to an understanding of the well established clinical observations that overeating by patients with cardiac disease often leads to discomfort and exacerbation of symptoms and

19. Gladstone, S. A.: Concerning the Mechanism of Production of the Korotkoff Sounds and Their Significance in Blood Pressure Determinations, Bull. Johns Hopkins Hosp. **44**:122, 1929.

occasionally to death. The last is sometimes erroneously ascribed to "acute indigestion." The physiologic basis for decreasing the size of the feeding in the treatment of heart failure, as exemplified by the usual cardiac low caloric diet, is also evident.

The low pulse rate (54, 58, 52 or 56 per minute) observed in normal young adults in the fasting condition and completely at rest is worthy of note. The pulse rate usually observed during routine examination is almost invariably considerably higher and indicates to what extent the subject's condition diverges from complete mental relaxation and physical rest.

In striking contrast to the general trend of changes in the blood pressure during digestion are those observed in patient E. F. (experiments 33 to 36). A marked fall is observed in both the systolic and the diastolic pressure during digestion. The extent of the change is practically the same, as observed on two successive days. Further studies will be necessary to determine the significance of these findings. The high cardiac index in patients with exophthalmic goiter [9] indicates the high cardiac output in that condition. Contrariwise, the cardiac index is very low in subject H. C. (experiments 26 to 29), whose hypothyroidism resulted from thyroidectomy for angina pectoris as recommended by Blumgart and his co-workers.[20] It may be noted in the case of the abnormal subject that while the average increase of oxygen consumption produced by digestion was 13 per cent, in the four observations on patients with exophthalmic goiter the average was only 7 per cent. A similar difference is noted in the results of the determinations of the cardiac output. This can be explained partly on the basis of the high initial figures during fasting, to which the increments are compared, but a better understanding of this difference will have to await a more extensive and detailed study.

CARDIAC OUTPUT AND BLOOD PRESSURE

Numerous investigators have studied the correlation of the cardiac or systolic output with measurable physical changes which occur during the heart's contraction in an attempt to use these changes as an index of the amount of blood discharged by the heart. The systolic output has been studied in relation to plethysmographic changes or changes in volume of the arm,[10] roentgen changes in the size of the heart,[21]

20. Friedman, H. F., and Blumgart, H. L.: Treatment of Chronic Heart Disease by Lowering Metabolic Rate; Necessity for Total Ablation of Thyroid, J. A. M. A. **102**:17 (Jan. 6) 1934.

21. Eyster, J. A. E., and Meek, W. J.: Instantaneous Radiographs of the Human Heart at Determined Points in the Cardiac Cycle, Am. J. Roentgenol. **7**:471, 1920.

changes in the blood pressure [22] and other changes. Of particular clinical interest are the studies correlating the systolic output with changes in the blood pressure, because of the ease and frequency with which the blood pressure is clinically determined. In 1904, Erlanger [23] found that the average of a large number of determinations of the volume of the arm and hand indicated that the pulse pressure and the changes in volume produced by the beat of the heart vary directly, "Exceptions, probably the result of local vaso-motor changes, are occasionally seen." Four years later, Dawson and Gorham [24] reported the results of simultaneous cardioplethysmographic measurements of the systolic output and manometric records of changes in the arterial blood pressure in anesthetized dogs before and during various procedures to alter the systolic output (stimulation of the central and peripheral branches of the vagus, stimulation of peripheral nerves, infusion of saline solution, bleeding, asphyxia and other methods). These authors concluded that "the pulse pressure is a reliable index of the systolic output." Regarding these two factors, first, it is apparent from a study of the graphs and tables presented by these workers that a change in one of these factors is usually attended by a change in the other in the same direction, i. e., an increase or a decrease. Secondly, it is equally apparent that the extent of the change in one factor is not equal or proportional to the extent of the change in the other; i. e., there is no simple linear relation between the two. Such relationship as may exist must be influenced by other factors, such as the variable elasticity of the aorta in different persons and also, in the same subject, the progressively decreasing distensibility of the aorta as it is stretched by a force which is serially increased by equal increments. In short, the more the aorta is stretched the harder it is to stretch it further. Fürst and Soetbeer [25] studied the relation between volumetric filling of the aorta and the pressure produced at various stages of distention. This was done by filling the aorta with fluid, after tying off all the branch vessels, and measuring the increase in pressure produced by forcing additional measured amounts of fluid into the aorta. These authors

22. Liljestrand, G., and Zander, E.: Vergleichende Bestimmungen des Minutenvolumens des Herzens beim Menschen mittels der Stickoxydulmethode, und durch Blutdruckmessung, Ztschr f. d. ges. exper. Med. **59**:105, 1928.

23. Erlanger, J., and Hooker, D. R.: An Experimental Study of Blood Pressure and Pulse Pressure in Man, Johns Hopkins Hosp. Rep. **12**:145, 1904.

24. Dawson, P. M., and Gorham, L. W.: The Pulse Pressure as an Index of the Systolic Output, J. Exper. Med. **10**:484, 1908.

25. Fürst, T. and Soetbeer, F.: Experimentelle Untersuchungen über die Beziehungen zwischen Füllung und Druck in der Aorta, Deutsches Arch. f. klin. Med. **90**:190, 1907.

offered the following formulas, which were empirically derived, as expressing the relationship of the various factors:

$$(1)\ V = \frac{P}{D + \frac{P}{3}}$$

$$(2)\ V = \frac{P}{D + \frac{P}{2}}$$

V, is the increase in volume (systolic output); P, the increase in pressure (pulse pressure), and D, the initial or minimal pressure (diastolic pressure). Although the original authors considered the second formula less satisfactory, Liljestrand and Zander,[22] in 1928, studied its variations as well as the changes in the cardiac and systolic output in four persons at rest, after eating, after the injection of epinephrine hydrochloride and during exercise. They found a satisfactory correlation between the systolic output as calculated from the second equation and the output as determined by the nitrogen monoxide method. In 1931, Schoenewald [26] studied the cardiac output and the changes in blood pressure during and following exercise in ten normal subjects and seventeen subjects with pathologic conditions and found that there was no constant relationship between the cardiac output as determined by the acetylene method and the output as calculated by the blood pressure formula. Bornstein, Budelmann and Rönnell [27] studied the changes produced by hot and cold baths on the cardiac output and blood pressure and observed that the "otherwise satisfactory" relationship between the pulse pressure and the stroke volume did not obtain. They believed that the disagreement was due at least partly to the particular influence of the hydrostatic pressure in baths.

Since I made several determinations of the blood pressure and cardiac output in the same patient, I can examine my data to determine whether in any given person the systolic output as found by the foreign gas method is proportional to the systolic output as calculated from the blood pressure. In order to compare my results with those of Liljestrand and Zander, I tabulated the numerical value for the systolic output as obtained from the formula $\frac{S-D}{\frac{1}{2}(S+D)}$, in which S is the systolic pressure in millimeters of mercury and D the diastolic pressure. This value, multiplied by the pulse rate—$P\ R \times \frac{S-D}{\frac{1}{2}(S+D)}$ — is a similar numerical measure of the cardiac output, as shown in the table. If a proportionality exists, the figures for the ratio, as shown in the table, should be con-

26. Schoenewald, G.: Ueber Beziehungen des Blutdrucks, besonders des Amplitudenfrequenzprodukts, zum Minutenvolumen des Herzens beim Menschen, Ztschr. f. d. ges. exper. Med. **79**:413, 1932.

27. Bornstein, A.; Budelmann, G., and Rönnell, S.: Minutenvolumen des Herzens in Bädern, Ztschr. f. klin. Med. **118**:596,1931.

stant or approximately so in any given subject. It is apparent that strict proportionality is not observed. Since the probable error in the determination of the cardiac output may be 10 per cent and the error in the measurement of the pulse rate and blood pressure somewhat less, real relationships may be obscured as a result of cumulative errors, especially since the changes of the phenomena measured as expressed in percentages are not great. As compared with the changes produced by exercise or recovery from exercise, the changes caused by digestion are less suitable because they are proportionately smaller, but are more suitable in that they change slowly and give the examiner time to perform the various maneuvers necessary to obtain the desired data or even to repeat the determinations under approximately the same conditions. I believe that the inadequacy of the formula is due in part, at least, to the variations in the ejection time of the heart, variations in local vasomotor responses, variations in the amount of blood escaping from the arterial tree peripherally during systole and other factors. One would scarcely hope to describe accurately the physical changes in a *variable* hemo*dynamic* system by means of a formula such as that of Fürst and Soetbeer, which is empirically derived from data obtained in a more or less *constant* hydro*static* set-up. Nevertheless, other conditions remaining the same, an increased systolic output increases the pulse pressure. In a variable cardiovascular system, however, where local and general changes and readjustments are constantly taking place, these may be sufficient not only to alter the relationship between the pulse pressure and the systolic output but even to reverse it, as the findings made thus far strongly suggest.

Since the general effect of digestion is to increase the cardiac output, pulse rate and pulse pressure, it becomes evident that in these observations a pulse rate $\times$ pulse pressure expression will increase with the cardiac output. Allowing for occasional experimental errors, this is seen to be true in practically all instances; i. e., the formula for the cardiac output indicates the direction of the change—an increase or decrease—as observed in the same person under approximately the same physical conditions, but the formula is not reliable as a quantitative measure of the change in the cardiac output and is even less reliable as a measure of the changes in the systolic output.

SUMMARY

The acetylene method was applied in a study of the effect of digestion on the cardiac output in forty-four determinations on twelve subjects, five of whom had normal cardiovascular systems while seven presented some structural or functional abnormality. A source of error in the method of analysis of gases as originally proposed is discussed; a cor-

rective procedure was applied, resulting in a tendency to increase the results for the cardiac output by approximately 3 per cent. As compared with the fasting condition, the effect of digestion on the circulatory system, as observed from one to three hours after taking a mixed meal of moderate size, consists in a slight increase in the systolic pressure and usually a less marked fall in the diastolic pressure, resulting in an increase in the pulse pressure. The cardiac output in the normal subject increased by from 11 to 47 per cent above the value during fasting, with an average increase of 25 per cent. In the abnormal subjects the increments varied by from 2 to 47 per cent, the average increase being 17 per cent. Several atypical responses in the subjects with pathologic conditions were noted.

The attempts to correlate changes in the blood pressure with changes in the systolic output are discussed, and the formula derived by Fürst and Soetbeer and tested with varying results by several authors was found on application to our data to possess only limited usefulness.

Dr. B. S. Oppenheimer's helpful suggestions and stimulating interest made these studies possible.

INCREASE IN CIRCULATION RATE PRODUCED BY EXOPHTHALMIC GOITER

COMPARED WITH THAT PRODUCED IN NORMAL SUBJECTS BY WORK

WALTER M. BOOTHBY, M.D.
AND
EDWARD H. RYNEARSON, M.D.
ROCHESTER, MINN.

In 1870, Frick pointed out that the output of the heart per minute could be determined from the difference in either the carbon dioxide or the oxygen tension of the blood before and after it passed through the lungs by direct determination of these gases in the arterial and venous blood. Subsequently, many attempts to adapt the Frick principle to the determination of the circulation rate in man were made by various investigators. The first of these attempts were based on equilibration of either the oxygen or the carbon dioxide in the lungs with the oxygen or the carbon dioxide in the blood, thus avoiding the dangers inherent in direct cardiac puncture as used originally. Bornstein, in 1910, suggested the use of high concentrations of nitrogen for equilibration, instead of carbon dioxide or oxygen, because it is an inert gas which does not enter into the various metabolic processes.

The next step was to use as the equilibrating medium not only an inert, but also a foreign, gas; nitrous oxide was suggested for this purpose by Markoff, Müeller and Zuntz, in 1911. The first successful method in which nitrous oxide was used was that developed by Krogh and Lindhard, which was reported in 1912. Krogh and Lindhard's method was first used in this country by Means and Newburgh [1] and by one of us (Boothby [2]); both investigations were reported in 1915. Means and Newburgh carried out studies on the effect of work on the circulation rate, and also made studies on patients with cardiac disease. Boothby limited his studies to the effect of work with himself as the subject and presented a chart illustrating the correlation

---

From the Section on Clinical Metabolism and the Division of Medicine, the Mayo Clinic.

1. Means, J. H., and Newburgh, L. H.: Studies of the Blood Flow by the Method of Krogh and Lindhard, Tr. A. Am. Physicians **30**:51, 1915.

2. Boothby, W. M.: A Determination of the Circulation Rate in Man at Rest and at Work: The Regulation of the Circulation, Am. J. Physiol. **37**:383 (May) 1915.

of the circulation rate, pulse rate, respiration rate, ventilation rate and mixed venous carbon dioxide and oxygen tensions for increasing amounts of work as measured by oxygen consumption. Since then only four studies have been made which can be readily utilized for comparison.

In figure 1 are plotted the circulation rates of different normal subjects at varying degrees of muscular work, as well as the values for the same subjects at rest, taken from the studies by Bock, Vancaulaert, Dill, Fölling and Hurxthal,[3] Boothby,[2] Christensen,[4] Douglas and Haldane,[5] Grollman [6] and Means and Newburgh.[1] To permit better comparison of the values for the circulation rate and oxygen consumption of persons of different sizes, the data of these observers have been recalculated and expressed as liters per square meter per minute and cubic centimeters of oxygen per square meter per minute. Fortunately, the height and weight of all the subjects were given by the respective authors, with the following exceptions: Dr. Grollman furnished the data for his subject, which were: height, 164 cm., and weight, 63.5 Kg. The values for Boothby's subject were: height, 166 cm., and weight, 47.7 Kg. Those for the subject J. H. M. of Means and Newburgh were: height, 175 cm., and weight, 73 Kg.

Although the amount of available data is still limited, it seems sufficient to confirm the conclusion of Boothby that there is an essentially linear relationship between the increase in the circulation rate and the increase in the oxygen consumption produced by work. The circulation rate when the subject is at rest under basal conditions (fig. 1) is approximately 2.2 liters per square meter per minute—a figure corresponding to the standard figures given by Grollman as the average obtained for fifty normal subjects. This increases approximately 88 cc. for each 100 cc. of increase in oxygen consumption per square meter per minute caused by work, as is shown by the heavy straight line in the middle. The two lighter parallel lines have been drawn to indicate that such a line can be only an approximation. The straight

---

3. Bock, A. V.; Vancaulaert, C.; Dill, D. B.; Fölling, A., and Hurxthal, L. M.: Studies in Muscular Activity: III. Dynamical Changes Occurring in Man at Work, J. Physiol. **66**:136 (Oct.) 1928.

4. Christensen, E. H.: Beiträge zur Physiologie schwerer körperlicher Arbeit, Arbeitsphysiol. **4**:128, 154, 175 and 499, 1931.

5. Douglas, C. G., and Haldane, J. S.: The Regulation of the General Circulation Rate in Man, J. Physiol. **56**:69 (Feb. 14) 1922.

6. Grollman, Arthur: (*a*) The Cardiac Output of Man in Health and Disease, Springfield, Ill., Charles C. Thomas, Publisher, 1932; (*b*) Physiologic Variations in the Cardiac Output of Man: XIII. The Effect of Mild Muscular Exercise on the Cardiac Output, Am. J. Physiol. **96**:8 (Jan.) 1931.

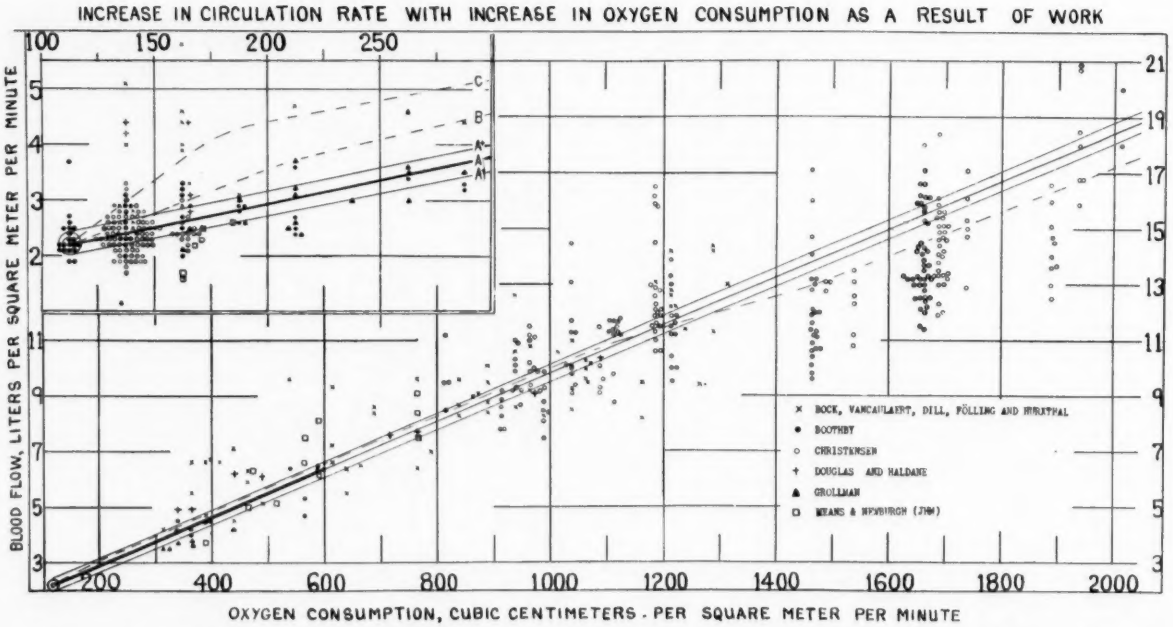

Fig. 1.—Curves showing the increase in the circulation rate with an increase in oxygen consumption as a result of work. The inserted chart is the enlarged scale for the lower part of the curve. *B* indicates the curve for exophthalmic goiter based on studies by Boothby and Fullerton and Harrop, and *C*, the curve for exophthalmic goiter based on studies by Liljestrand and Stenström.

line as reproduced here is the original one given by Boothby, except that it has been recalculated on the basis of surface area. Although Boothby's graph was based on degrees of work representing an oxygen consumption up to only 600 cc. per square meter per minute, it can be extrapolated to extreme degrees of work with little error. It is apparent, however, that this straight line does not exactly represent the entire data. For light work, the data for which are plotted at the lower end of the chart, there is an indication of a slight increase in the circulation rate, which is, however, practically negligibly greater than that indicated by a straight line. On the other hand, with moderately severe work, corresponding to an oxygen consumption of more than 1,200 cc. per square meter per minute, there is an indication of slightly better utilization of the carrying power of the blood, which results in a slight, but appreciably slower, rate of increase in the circulation rate. These slight departures from the straight line have been indicated on the chart by the free-hand drawing of an S-shaped curve in a broken line; the data are not large enough or sufficiently homogeneous to justify construction of such a curve by the method of least squares.

Bock and his associates, as well as Douglas and Haldane, determined the circulation rate by equilibration of the carbon dioxide in the lungs with that of the venous blood, whereas the other investigators used either the nitrous oxide method of Krogh and Lindhard or Grollman's modification, using acetylene as the equilibrated gas. Both methods give essentially similar results except at the lower end of the curve, for very light work, where the fallacies inherent in the carbon dioxide method may easily cause proportionately larger errors.

It is of interest to compare the increase in the circulation rate that accompanies the increased oxygen consumption resulting from work by normal subjects with the increase in the circulation rate and oxygen consumption that occurs in persons who have exophthalmic goiter.

Plesch and Davies, Meakins and Long and Bansi showed by other methods that the circulation rate was increased in exophthalmic goiter. In 1915, Liljestrand and Stenström,[7] using the nitrous oxide method of Krogh and Lindhard, demonstrated an increase in the circulation rate in exophthalmic goiter; they made seventy observations on eight women and three men. The increase in the circulation rate found by them was surprisingly large, in many instances even exceeding the increase in oxygen consumption, so that the difference in the arterial and venous oxygen was unchanged or even occasionally decreased.

7. Liljestrand, G., and Stenström, N.: Clinical Studies on the Work of the Heart During Rest: I. Blood Flow and Blood Pressure in Exophthalmic Goiter, Acta med. Scandinav. **63**:99, 1925.

Recently, Fullerton and Harrop [8] made a similar study; they used the nitrous oxide method with the simplifications introduced by Grollman.[6] They reported eighty-six determinations on five women and three men, with an average basal metabolic rate of 30.3 per cent above normal and with a circulation rate 41.5 per cent above a normal value of 2.2 liters per square meter per minute. Following the administration of a solution of iodine and thyroidectomy, both the metabolic and the circulation rate returned close to the normal standard figure.

During the last two years we have carried out a series of one hundred and sixty determinations of the circulation rate of seven women and four men who had exophthalmic goiter; in these determinations we used acetylene, as suggested by Grollman, instead of nitrous oxide because it is much more simple to analyze. The results for the basal metabolic rate, oxygen consumption per minute and blood flow in liters per square meter per minute are given in the table, and every determination made on each subject is included. In all experiments on the circulation rate there is quite a spread in the determinations made under apparently identical conditions, even with good technic, and in determinations on patients with exophthalmic goiter this spread is definitely larger than the same observers obtained for normal subjects. Therefore, this increased divergence in exophthalmic goiter cannot necessarily be attributed solely to faulty technic but may represent a greater variability in, or instability of, the circulation rate in this disease; at least, it does not seem safe to us to exclude any of our own observations. Although the variations do not greatly affect the general picture of the average circulation rate in exophthalmic goiter if a sufficient number of determinations are made, the discrepancy in the reported results of determinations in the same case, as can be seen in the tabular presentation of the data, nevertheless precludes the utilization of the method for diagnostic purposes. On the other hand, our data, in conjunction with similar observations reported in the literature, enable one to understand better the effect of the disease on the heart and circulation rates, with the resultant clinical phenomena.

We have plotted, in figure 2, against oxygen consumption per square meter per minute our own results of studies of the circulation rate in liters per square meter per minute made on patients with exophthalmic goiter and, in addition, the observations of Liljestrand and Stenström and of Fullerton and Harrop, recalculated on the square meter basis. We have also drawn in the smoothed curve for the increases in the circulation rate due to work, as obtained from figure 1. In order to aid in demonstrating the differences, as well as the similarities, in these

8. Fullerton, C. W., and Harrop, G. A., Jr.: The Cardiac Output in Hyperthyroidism, Bull. Johns Hopkins Hosp. **46**:203, 1930.

Circulation Rate in Exophthalmic Goiter: Essential Data on Seven Women and Four Men

	Date, 1932	Weight, Kg.	Basal Metabolic Rate	Oxygen Consumption, Cc. per Sq.M. per Minute	Blood Flow, Liters per Square Meter per Minute		
					1	2	3
Married woman; age, 48; height, 161 cm.	11/19	62.2	+30	268	2.8	3.3	...
	11/21	61.6	+31	267	4.0	2.8	...
	11/23	61.4	+34	276	2.6	2.9	...
	11/24	61.2	+32	272	2.5	...	...
	11/26	61.3	+30	267	3.1	...	...
	11/28	61.6	+39	284	3.1	2.6	...
	11/30	60.5	+34	272	2.8	3.1	...
	12/ 2	60.5	+32	267	2.2	2.8	...
	12/ 3	60.7	+34	272	3.8	3.1	...
	12/ 5	60.7	+25	251	3.5	2.6	...
	12/ 8	60.7	+26	258	2.6	2.3	...
	12/ 9	Thyroidectomy					
	12/22	59.0	+ 2	202	2.3	...	...
	12/27	60.4	— 7	187	2.1	2.2	...
Unmarried woman; age, 25; height, 167 cm.	9/13	47.2	+46	284	3.7	...	...
	9/24	48.0	+19	229	2.5	...	...
	9/27	Thyroidectomy					
	10/ 6	45.7	+ 1	192	2.7	2.7	...
	10/10	46.0	+ 3	198	2.8	...	...
	10/12	46.5	— 2	176	1.9	2.6	...
	10/19	46.6	—11	170	2.3	...	...
Unmarried woman; age, 23; height, 159 cm.	9/24	53.2	+55	314	3.3	4.3	...
	9/27	52.7	+45	295	3.7	3.0	...
	9/29	53.1	+38	280	2.9	...	...
	9/30	53.1	+28	259	3.2	3.2	3.2
	10/ 3	54.2	+34	272	3.3	3.1	...
	10/ 4	Thyroidectomy					
	10/13	53.4	+13	225	2.8	3.0	...
	10/17	54.7	— 1	196	2.1	2.1	...
	10/20	55.2	+ 6	214	2.2	2.4	...
	1933						
Man; age, 27; height, 168 cm.	6/ 8	59.2	+90	440	4.0	...	...
	6/14	57.5	+77	403	3.9	...	...
	6/16	Thyroidectomy					
	6/26	55.0	+15	254	2.8	...	...
	7/ 5	59.8	0	223	2.2	...	...
	1932						
Man; age, 43; height, 169 cm.	11/ 8	59.4	+60	360	3.4	...	...
	11/10	60.3	+46	332	4.2	5.0	...
	11/11	60.0	+43	325	2.6	4.0	...
	11/14	58.9	+26	280	3.3	...	...
	11/16	58.1	+29	293	3.1	3.6	...
	11/18	58.1	+28	286	2.5	...	...
	11/18	Thyroidectomy					
	11/26	58.4	+19	266	2.5	2.7	...
	11/29	58.2	+ 4	229	2.8	2.4	...
Married woman; age, 44; height, 159.5 cm.	10/22	64.3	+88	394	4.6	...	...
	10/24	64.7	+70	354	4.0	4.2	...
	10/26	63.8	+57	329	3.4	3.2	...
	10/28	64.3	+56	321	4.3	4.5	...
	10/29	64.2	+51	316	4.1	...	...
	10/31	64.3	+47	305	3.6	4.2	...
	11/ 2	63.7	+42	296	3.6	3.0	...
	11/ 4	63.5	+39	290	2.7	4.1	...
	11/ 7	64.7	+42	291	3.2	4.0	...
	11/ 9	64.4	+45	302	3.2	3.0	...
	11/10	64.7	+40	289	3.3	3.6	...
	11/11	Thyroidectomy					
	11/23	62.8	+13	227	2.5	2.4	...
	11/25	63.5	+14	233	4.6	3.9	...
	11/28	63.7	+ 4	214	2.6	1.8	...

Circulation Rate in Exophthalmic Goiter: Essential Data on Seven Women and Four Men—Continued

	Date, 1932	Weight, Kg.	Basal Metabolic Rate	Oxygen Consumption, Cc. per Sq.M. per Minute	Blood Flow, Liters per Square Meter per Minute		
					1	2	3
	1933						
Unmarried woman;	10/ 6	57.8	+42	290	2.3	...	...
age, 42;	10/12	59.0	+36	284	3.3	2.3	...
height, 165.5 cm.	10/13	59.0	+30	267	2.6	...	...
	10/16	59.0	+25	258	3.0	...	...
	10/19	60.1	+11	228	1.4	...	...
	10/20	Thyroidectomy					
	10/30	59.5	+ 2	212	2.6	...	...
	11/ 1	59.8	0	208	2.0	...	...
	11/ 6	60.0	— 5	196	2.4	2.1	...
	11/ 8	57.9	— 6	191	2.4	...	...
	11/13	57.9	—12	175	2.1	...	...
Unmarried woman;	9/17	64.6	+74	367	3.9	3.3	...
age, 22;	9/28	66.3	+49	317	2.6	3.5	...
height, 160 cm.	11/ 4	65.6	+68	358	3.7	3.5	...
	11/ 7	65.7	+52	325	2.7	...	...
	11/10	Thyroidectomy					
	11/22	66 5	+24	261	2.4	2.2	...
	1934						
Man; age, 32;	3/19	53.5	+27	286	3.4	2.2	...
height, 177.5 cm.	3/21	54.0	+22	274	3.3	2.5	...
	3/23	54.4	+13	256	3.3	2.7	...
	3/26	55.1	+18	272	3.2	2.4	...
	3/28	55.2	+17	268	2.4	...	...
	3/29	Thyroidectomy					
	4/ 9	56.0	— 7	216	2.6	...	...
	4/11	56.0	—12	199	2.6	...	...
	1932						
Man; age, 47;	11/ 1	75.4	+45	370	2.5	...	...
height, 177 cm.	11/ 4	75.0	+44	362	3.7	...	...
	11/ 5	74.3	+45	368	2.4	2.8	...
	11/ 7	74.4	+37	348	3.2	2.3	...
	11/ 8	74.0	+31	333	3.0	2.4	...
	11/ 9	74.1	+27	320	2.5	2.9	...
	11/11	74.7	+21	304	3.0	...	...
	11/11	Thyroidectomy					
	11/19	72.3	+ 5	268	2.0	2.7	...
	11/22	73.6	— 3	242	2.3	2.0	...
	1933						
	1/31	82.2	—27	196	3.7	2.5	...
	2/14	84.1	—17	216	1.9	2.7	...
	1932						
Married woman;	9/14	55.8	+39	274	3.0	...	...
age, 48;	9/16	55.5	+41	280	3.1	3.4	...
height, 159 cm.	9/19	54.4	+31	258	3.3	2.9	...
	9/20	54.7	+32	260	4.5	3.4	3.5
	9/21	54.9	+32	260	3.0	3.4	...
	9/22	55.0	+20	234	2.5	...	...
	9/23	55.5	+31	263	3.3	3.5	...
	9/26	55.9	+23	247	2.6	3.0	...
	9/27	Thyroidectomy					
	10/12	55.3	— 1	195	2.3	2.6	...
	10/14	55.5	0	198	2.2	2.2	...
	10/17	56.8	— 4	193	2.2	...	...

curves for both work and exophthalmic goiter, we have drawn in on the enlarged section of the work scale in figure 1 for the range of work comparable to the increases in oxygen consumption in exophthalmic goiter the curves for exophthalmic goiter obtained in figure 2.

A study of figure 2 shows the following interesting points: 1. There is a marked increase in the circulation rate with increasing oxygen consumption in exophthalmic goiter, as is shown by individual observations in all three series of experiments, which is definitely much greater than that which occurs in normal subjects as a result of work; this is indicated by the fact that nearly all the individual observations lie above the mean curve for work. 2. The average value for the circulation rate with increasing oxygen consumption in exophthalmic goiter, as found by us, agrees closely with the average value found by Fullerton and Harrop. Although our individual determinations show a slightly greater spread than theirs, the mean values of both series are in such close agreement that we have combined these two sets of data to form the group of mean values shown in the upper part of figure 2. 3. The means for the group of the observations made by Liljestrand and Stenström, as shown clearly in the upper half of figure 2, indicate a much more rapid and a greater increase in the circulation rate for a given increase in oxygen consumption than do the means for the group of our own data combined with those of Fullerton and Harrop. Curves have been drawn in on the upper half of figure 2 to represent the general increase in the circulation rate with the increase in the metabolic rate, as measured by an increase in oxygen consumption, for both the Swedish series and the combined American series. In addition, the curve representing the increase in the circulation rate of normal persons accompanying increased oxygen consumption resulting from work is again reproduced to aid in differentiating the responses by the circulation in the two conditions.

As all three series of the observations on exophthalmic goiter which have just been referred to were made in well equipped laboratories and by observers with considerable experience in experiments of this type, the general accuracy of the three series cannot be questioned, least of all those of Liljestrand and Stenström of the Karolinska Institute of Stockholm.

What, then, can explain the average agreement of our results with those of Fullerton and Harrop and the markedly greater increase in the circulation rate found by Liljestrand and Stenström? First, we think that there is no question that there is a progressive increase in the circulation rate in exophthalmic goiter corresponding to the severity of the disease, as measured by an increase in oxygen consumption. Second, this increase in the circulation rate is greater than that which occurs among normal subjects as the result of a corresponding increase

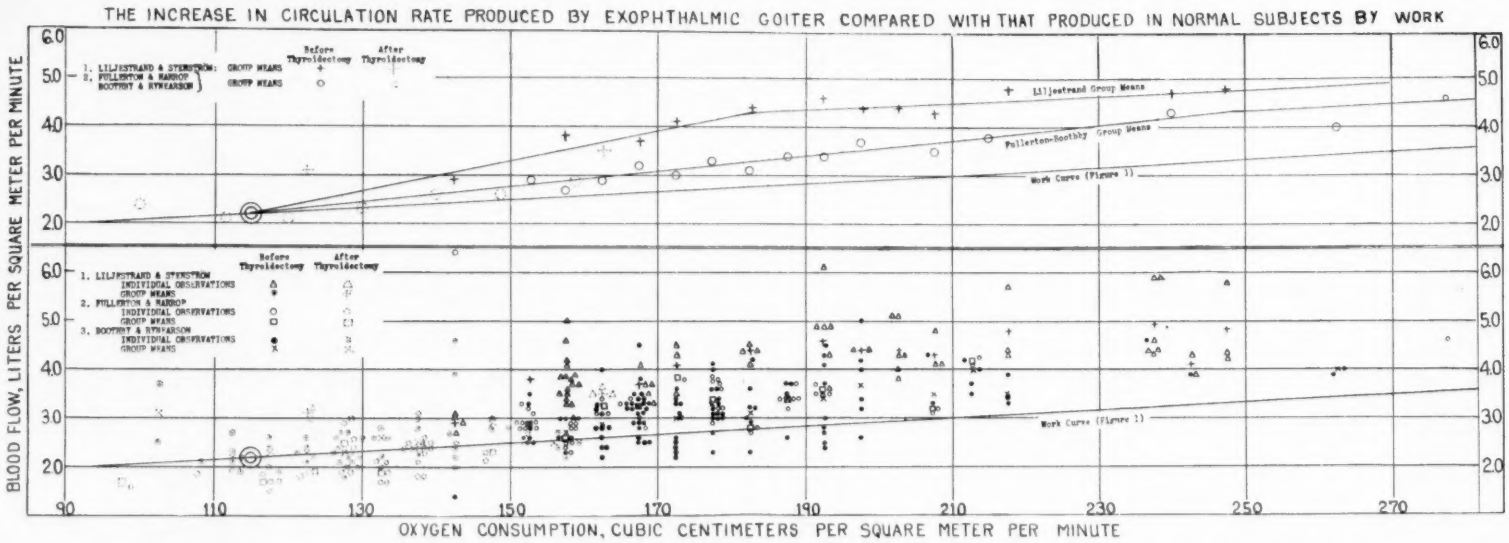

Fig. 2.—Curves showing the increase in the circulation rate produced by exophthalmic goiter, compared with that produced in normal subjects by work. The values are plotted about the mean curve for the increase in the circulation rate, due to work, taken from figure 1. The upper chart shows the curves for the mean values for the two groups considered, which fall above the mean curve for the increase in the circulation rate due to work.

in oxygen consumption due to work. Third, all the patients in our series, as well as all but one patient in Fullerton and Harrop's series, received compound solution of iodine U. S. P., usually before even the first determination was made. On the other hand, the patients observed by Liljestrand and Stenström did not receive iodine in any form. It is now well recognized that the administration of iodine usually decreases the basal metabolic rate and, at the same time, markedly quiets the forcible and tumultuous beating of the heart. Often the powerful action of the heart of the patient with exophthalmic goiter before the administration of iodine is so violent as to shake the bed; usually a definite capillary pulse can be seen in the finger-nails, and this is frequently accompanied by secondary manifestations of cardiac fatigue. All these manifestations usually decrease markedly after effective medication with iodine, as do also the typical nervous manifestations of the disease. Therefore, we believe that the greater increase in the circulation rate observed by Liljestrand and Stenström, as compared with the observations in the other two series, represents a true difference and is the result of an abnormal increase in the circulation rate relative to the increase in oxygen consumption of patients with exophthalmic goiter who do not receive iodine. Iodine, therefore, not only tends to decrease the rate of heat production in exophthalmic goiter but also decreases the excessive circulation rate of the patient with the typical, severe form of the disease who has not been treated previously with iodine, although it may not decrease it to the level found for the increase in the circulation rate with increased oxygen consumption produced in normal persons by work.

In both our series and Fullerton and Harrop's series there are data on a considerable number of observations following thyroidectomy. These are also plotted in figure 2 and can be distinguished from those made before thyroidectomy by the fact that dotted symbols are used. Nearly all the mean values of the group are seen to lie close to the line of the circulation rate during work, even if the postoperative determinations were made before the oxygen consumption and the circulation rate returned to the normal basal level. This indicates that even if, at the time of observation after thyroidectomy, the heat production and the circulation rate have not returned completely to average normal values, nevertheless the discrepancy between the increased circulation rate and the oxygen consumption in exophthalmic goiter, as compared with the increase due to work, has largely disappeared. Liljestrand and Stenström likewise made a few observations after thyroidectomy; the circulation rates of their patients, however, did not return to the anticipated values. Clinically, it is well known that the return to normal, both in the metabolic rate and in the tumultuous action of the heart, is less rapid and on the average less complete immediately following

thyroidectomy in patients who are not under the influence of iodine as compared with those who have had ample and effective treatment with iodine both before and after operation.

SUMMARY

The circulation rate is increased in exophthalmic goiter. On the average, the greater the intensity of the disease, as measured by oxygen consumption, the greater is the increase in the circulation rate.

The increase in the circulation rate in patients with exophthalmic goiter who are not treated with iodine, according to the investigations of Liljestrand and Stenström, is much greater than that which occurs in normal persons as the result of an increase in oxygen consumption due to work.

The relative increase in the circulation rate for a given increase in oxygen consumption is definitely less in patients who are treated with iodine than in those who have not received iodine. However, even under these conditions the increase in the circulation rate was, on the average, both in our cases and in those of Fullerton and Harrop, slightly greater than that produced in normal persons by a degree of work that caused a similar increase in oxygen consumption.

These facts suggest the hypothesis that in exophthalmic goiter, especially when the patient is not treated with iodine, there is present in the system a peculiar circulatory stimulant that causes a greater increase of the circulation rate than occurs in a normal subject as the result of a corresponding increase in oxygen consumption due to work. In exophthalmic goiter either this peculiar circulatory stimulant is decreased in amount or its effectiveness is lessened by effective medication with iodine.

INCIDENCE OF BACTEREMIA IN THE PNEUMONIAS AND ITS RELATION TO MORTALITY

JESSE G. M. BULLOWA, M.D.
Clinical Professor of Medicine, New York University, University and Bellevue Hospital Medical College; Visiting Physician, Harlem Hospital

AND

CLARE WILCOX
Bacteriologist, Littauer Pneumonia Research Fund of New York University, Harlem Hospital Station

NEW YORK

The recovery of pneumococci from the blood stream during the course of pneumococcic pneumonia may be prima facie evidence that the protective mechanism which prevents or overcomes bacteremia is at least partially in abeyance. Whether recovery or death will be the outcome in pneumococcic pneumonia depends to a great extent on whether the protective mechanism alone, or aided by serum, suffices to prevent an increase in the number of organisms or to clear the blood of pneumococci after it has been invaded.

During the past seven and a half years we have regularly taken blood cultures in our study of pneumonia at Harlem Hospital. We have selected for presentation the results of our work during the years between July 1, 1928, and June 30, 1933, because: (1) Rosenblüth [1] has already presented our material with respect to bacteremia during the first two years, and (2) during this later five year period we have been able to study the newer types of pneumococci, as segregated and numbered by Georgia Cooper. Not only have we subdivided the cases formerly classed as group IV (originally termed by us the miscellaneous or "x" group), but we have also separated from the organisms elsewhere and formerly included by us as the pneumococcus type II, the subtype IIa of Avery, designated in the classification of Cooper as type V, and the Thomas strain of Sugg, Gaspari, Fleming and Neill, formerly included in type III and now designated type VIII.

Read before the Section on Medicine of the New York Academy of Medicine, Oct. 19, 1933.

This study received financial support, in part, from the Metropolitan Life Insurance Company.

From the Littauer Pneumonia Research Fund of New York University and the Medical Service, Harlem Hospital (Department of Hospitals).

1. Rosenblüth, M. B.: Relation of Bacteremia in Lobar Pneumonia to Prognosis and Therapy, J. A. M. A. **90**:1357 (April 28) 1928.

1351

In most cases, positive blood cultures give unequivocal evidence of the type of pneumococcus responsible for the illness, and the disappearance of bacteremia in response to treatment may be a real measure of efficient specific therapy. In cases in which invasion of the blood continues in spite of therapy the illness is almost uniformly fatal. On this account the occurrence of bacteremia is worthy of particular study. We shall present our observations with respect to the occurrence of bacteremia and the mortality in the different types in a series of graphs.

PROCEDURE AND CRITERIA

The criteria for the diagnosis of pneumonia and of bacteremia, as used at Harlem Hospital, must first be given if these statistics are to be evaluated properly and compared with others. The clinical diagnosis of pneumonia is based on the history and physical findings, including roentgenography or fluoroscopy and the white blood cell count. If recovery occurs, diagnostic importance is attached to the clinical course and laboratory observations; if death, to the clinical course, autopsy and postmortem cultures. In compiling statistics or at the termination of illness, doubtful cases and those incorrectly diagnosed are removed from the series, but no cases of pneumonia are removed because the patients were moribund or died shortly after admission. The diagnosis of pneumococcic pneumonia depends on recovering a bile-soluble diplococcus from the sputum, pharyngeal or laryngeal culture, lung juice [2] culture as obtained by transpleural aspiration in broth and/or blood culture. Sputum or other cultures are studied directly and by injection into mice. The typing is by a specific capsule-swelling reaction with serum of immune rabbits (Neufeld) or by the stained slide technic (Sabin) [3] of agglutination of peritoneal exudate. The organism responsible for septicemia in the mouse is studied in a culture of the heart blood and in a culture from the brain tissue of the mouse.

A blood culture is taken on admission in all cases and is repeated: (1) if the temperature continues to be high, or falls, and the pulse rate continues to be rapid; (2) if the temperature rises and the pulse rate becomes more rapid, and (3) if there is a marked change in the condition of the patient. Three cubic centimeters of blood is drawn; of this 1 cc. is cultured in 50 cc. of broth (p_H from 7.4 to 7.6, previously tested for growing the pneumococcus well), and 1 cc. is cultured in each of two plain agar plates. The blood is expelled into the Petri dish, the melted agar (temperature 41 C.) poured and the whole mixed. Cultures are made post mortem (usually within a half hour) from consolidated lung tissue, from blood from the heart and frequently from the cerebrospinal fluid.

Alternate patients with pneumonia receive probative serum—two doses (5 and 10 cc.) of duovalent type I and type II serum, with from 1,500 to 2,500 units of each type per cubic centimeter. In all cases of type I the patients received serum unless in collapse and moribund or in a postcritical condition with agglutinins for type I (slide technic) present in the blood. In all cases of type II in which probative serum has been given the patients continue to receive duovalent serum. In other type II cases the patient receives serum if he has been admitted after a

2. The term lung juice was used to describe the material obtained by transthoracic aspiration of the lung. Its constituents are tissue, blood, lymph and exudate, if any.

3. Sabin, A. B.: Proc. Soc. Exper. Biol. & Med. **26**:492, 1929.

nonserum-treated patient with a type II infection. In other types, serum is given in alternate cases of the type involved, if serum for the type is available.

Pneumonia is regarded as not due to a pneumococcus if there is failure to obtain pneumococci on careful, repeated examinations of the sputum, lung juice and blood, or if another etiologic agent is found. If pneumococci fail to grow in the blood during life, or soon after death, the case is counted as nonbacteremic. The recovered pneumococcus is regarded as causally related to the pneumonia: (1) when pneumococcus is found in good sputum or in laryngeal or pharyngeal mucus on a swab; (2) when the pneumococcus is present in lung juice obtained by suction of the lung; (3) when the pneumococcus grows in a blood culture, and (4) when agglutination, previously absent, develops in the blood for the type of pneumococcus recovered in the discharges.

DISTRIBUTION OF TYPES

In their classic studies published in 1917, as monograph 7 of the Rockefeller Institute, Avery, Chickering, Cole and Dochez found only 20 per cent of cases of pneumonia in their group or type IV. Cole, in Nelson "Loose-Leaf Medicine," subsequently reported a slightly larger number of cases in this group. Cecil, at Bellevue Hospital, and also Blake, in New Haven, classified 34 and 35 per cent of their cases as belonging in group IV.

In the past five years, only 41 per cent of our cases were of types I, II and III; the remaining 59 per cent included: (1) types IV to XXXII (Cooper), (2) our present type x and (3) multiple infections. Our percentage of cases of types I, II and III was even lower than that in the report of Rosenblüth,[1] which embodied the first two years of our experience.

A comparison of our present statistics with those of Rosenblüth disclosed a reduction of pneumococcus type I cases in our series which we do not attempt to explain. We found a decline in the incidence of bacteremia in type I cases from 35 to 27.4 per cent; this is probably due to earlier and more frequent administration of serum. There is also a reduction of the type II and type III cases, but there is an increased incidence of their bacteremias. In type II, the number of cases fell from 19 to 9.4 per cent, and the cases of bacteremia increased from 31 to 38.6 per cent. In type III, the relative number of cases fell from 13.2 to 8.9 per cent, and the bacteremic incidence increased from 25 to 29.6 per cent. In the type II cases, the reduction may be explained by the exclusion of the subtype IIa of Avery as type V, and in the case of type III, the segregation from type III of the cases due to the Thomas strain of Sugg and his co-workers, as type VIII.

THE DECLINE OF GROUP X (UNDESIGNATED TYPES)

The comparatively large number of cases now included in the newer types of Cooper and in the smaller x group and the increased bacteremic incidence in this section make it worth while to analyze these cases

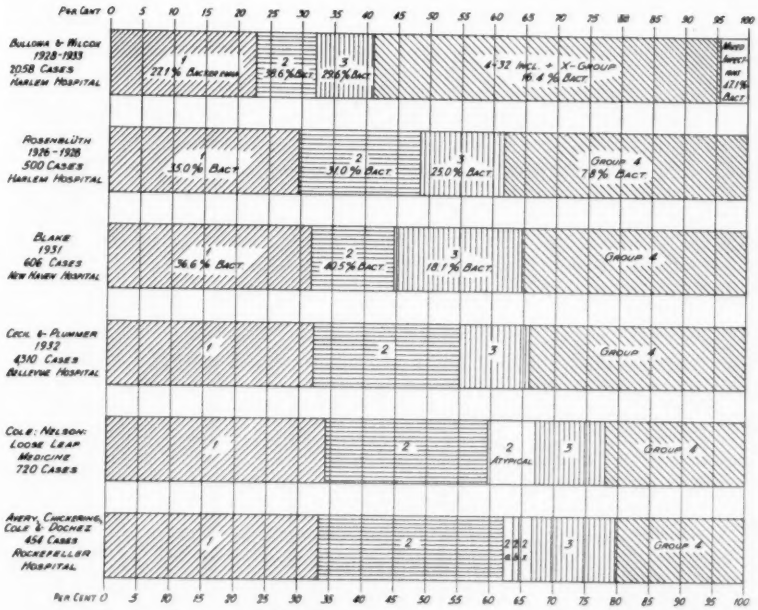
PER CENT 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
BULLOWA & WILCOX 1928-1933 2058 CASES HARLEM HOSPITAL
1 27.1% BACTEREMIA
2 38.6% BACT.
3 29.6% BACT.
4-32 INCL. + X-GROUP 16.4% BACT.
MIXED INFECTIONS 47.1% BACT.
ROSENBLÜTH 1926-1928 500 CASES HARLEM HOSPITAL
1 35.0% BACT.
2 34.0% BACT.
3 25.0% BACT.
GROUP 4 7.8% BACT.
BLAKE 1931 606 CASES NEW HAVEN HOSPITAL
1 36.6% BACT.
2 40.5% BACT.
3 18.1% BACT.
GROUP 4
CECIL & PLUMMER 1932 4310 CASES BELLEVUE HOSPITAL
1
2
3
GROUP 4
COLE: NELSON: LOOMIS LEAP MEDICINE 720 CASES
1
2
2 ATYPICAL
3
GROUP 4
AVERY, CUCKERING, COLE & DOCHEZ 454 CASES ROCKEFELLER HOSPITAL
1
2
2 2 2 2 & 3
3
GROUP 4
PER CENT 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100

Chart 1.—Comparison of the distribution of types of pneumococcic pneumonia and of bacteremia in each in reported studies.

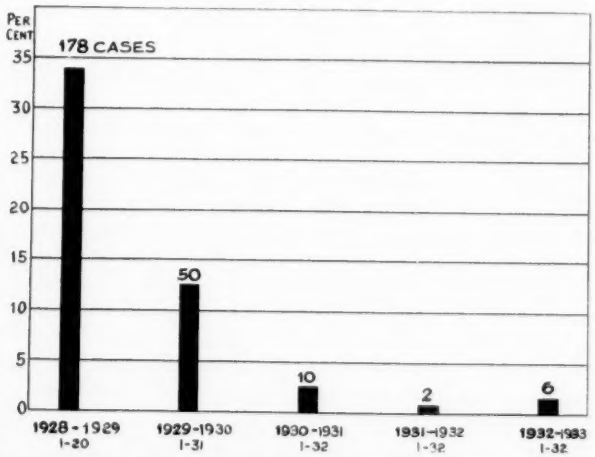

Chart 2.—Decline of the x group in 2,058 cases of adult pneumococcic pneumonia. Each block indicates the percentage of cases unclassified in one year. The figures under the year reveal the number of types for which typing was done in that year. Above each block is the number of unclassified or x group cases each year.

further. In our series, the number of cases of bacteremia in what was formerly called group x was 16.5 per cent; in Rosenblüth's, it was 7.8 per cent.

In the last five years the x group has diminished, so that it now comprises only 3 per cent of our cases annually. In the first year of these studies, 1928-1929, we were typing to type XX (Cooper); that year there were one hundred and seventy-eight cases in the x group. During the past year there were only six cases which did not fall into the thirty-two Cooper types, and in the previous year, two cases. Still more interesting has been the course of the frequency of invasion of

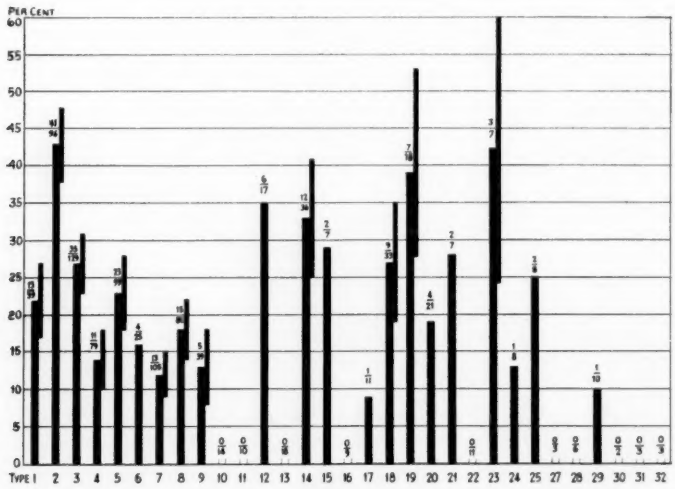

Chart 3.—Incidence of cases of bacteremia in which no serum was given, numerically arranged. The standard error is indicated as a bayonet in types in which 18 or more cases were observed. The standard error is given in the text for types in which there were fewer than 18 cases. The standard error is calculated as $E = \sqrt{\frac{pq}{n}}$ when E equals the standard error; p, the rate of bacteremia invasion; q, $1 - p$, and n, the number of cases observed. The numerator of each fraction indicates the number of bacteremic cases, the denominator the total number of cases.

the blood. In 1928-1929 there were eleven cases of invasion by unclassified organisms; in 1929-1930 there were two; in 1930-1931, one; in 1931-1932, none, and in 1932-1933, none. In the entire five year period there were four hundred and twenty-seven cases of bacteremia. Fifteen, or 3.5 per cent, were not typed. This decline in the unclassified cases has been experienced wherever similar studies have been made.

INVASION OF THE BLOOD IN CASES FORMERLY IN GROUP IV ("X" OR MISCELLANEOUS)

There is much misinformation concerning the virulence of cases formerly included in group IV. We have prepared a graph (chart 3)

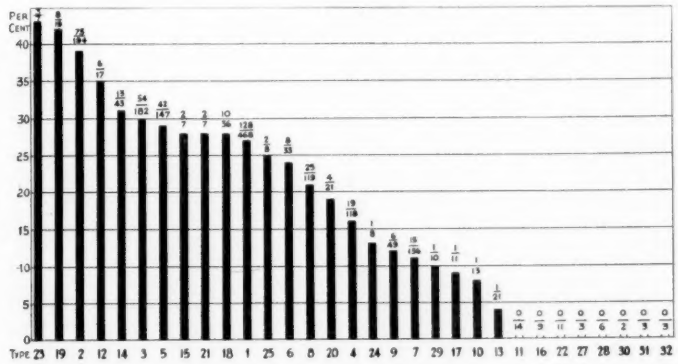

Chart 4.—Incidence of bacteremia in the order of percentage frequency of cases of bacteremia in pneumonia of each type. The numerator indicates the number of bacteremic cases, the denominator the total number of cases.

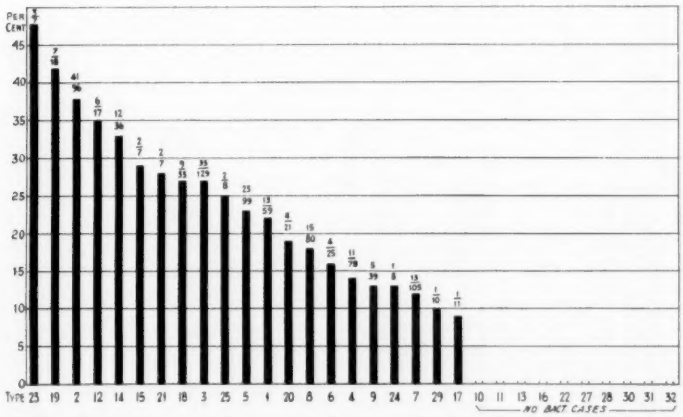

Chart 5.—Incidence of bacteremia in the order of percentage frequency of cases of bacteremia in pneumonias of each type. Only cases in which no serum was given are included. The numerator indicates the number of bacteremic cases, the denominator the total number of cases.

in which the bacteremic incidence for each type is given. A glance shows that the bacteremic incidence varies, and that in some the incidence is greater than the incidence in types I, II or III. The standard error

of the observations has been computed and attached as a bayonet to the top of the blocks whenever more than eighteen cases have been observed. In each instance the fraction above the block shows the num-

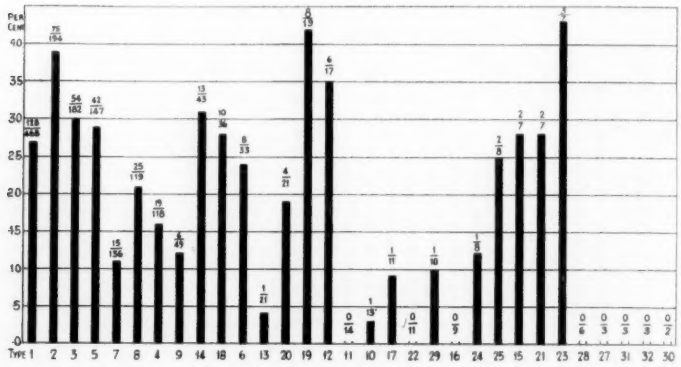

Chart 6.—Incidence of bacteremia in the order of numerical frequency of the occurrence of bacteremia in pneumonia of different types. All patients, those treated by serum and those not treated by serum, are included. The numerator indicates the number of bacteremic cases, the denominator the total number of cases.

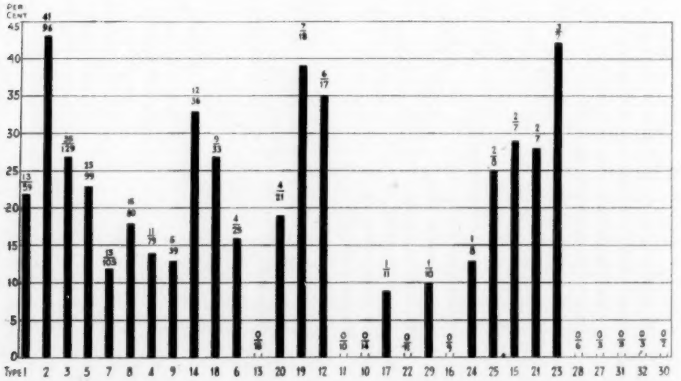

Chart 7.—Incidence of bacteremia in the order of numerical frequency of the occurrence of bacteremia in pneumonia of different types. Only cases in which no serum was given are included. The numerator indicates the number of bacteremic cases and the denominator the total number of cases.

ber of bacteremic cases as numerator and the total number of cases of the type as denominator. In some types, bacteria have not as yet been recovered by us from the blood stream of a patient. For types with

fewer than eighteen observed cases the standard error is as shown in the table. It should be emphasized also that in cases in which no bacteremia has been observed as yet, the standard error may be very large, especially when there are few cases.

Chart 3 shows that type V, formerly included in type II, is less invasive than type II, and that type VIII is less invasive than type III, with which it was formerly combined. Of all the types which do invade the blood, type XXIII is apparently most invasive, with 42.8 per cent. Some of the types most frequently encountered have a lower bacteremic incidence than those which appear infrequently. The infrequently encountered diseases may be more fatal when they occur. Accordingly, it is important to have available specific serum for the infrequent, but fatal, types.

Standard Error for Types with Fewer than Eighteen Cases

Type	Bacteremia, per Cent	Standard Error, per Cent
VI	16.0	7.3
XII	35.0	11.0
XV	28.5	17.0
XVII	9.0	8.6
XX	19.0	8.7
XXI	28.0	17.0
XXIV	12.5	20.0
XXV	25.0	15.0
XXIX	10.0	3.0

To judge the importance of each type of pneumococcus as a cause of bacteremia, the types are arranged in the order of percentile frequency of occurrence of cases of bacteremia in charts 4 and 5, and in charts 6 and 7, in the order of frequency in which the pneumococci are encountered in the blood. Charts 4 and 6 give all cases, and charts 5 and 7 only cases in which no serum was given.

Although less invasive than at least ten other types of pneumococci, the type I pneumococcus is the organism most frequently encountered in the blood stream of patients suffering from pneumococcic pneumonia. Type II is the second most frequently encountered organism in the blood of patients with pneumococcic pneumonia. Although it invades the blood of more than 40 per cent of its victims, in percentage incidence of bacteremia it is only third among the thirty-two types. Types XXIII and XIX invade the blood more frequently than type II. Type III, though ranking third in the order of frequency in the number of cases encountered, is ninth in the order of percentage occurrence of bacteremia.

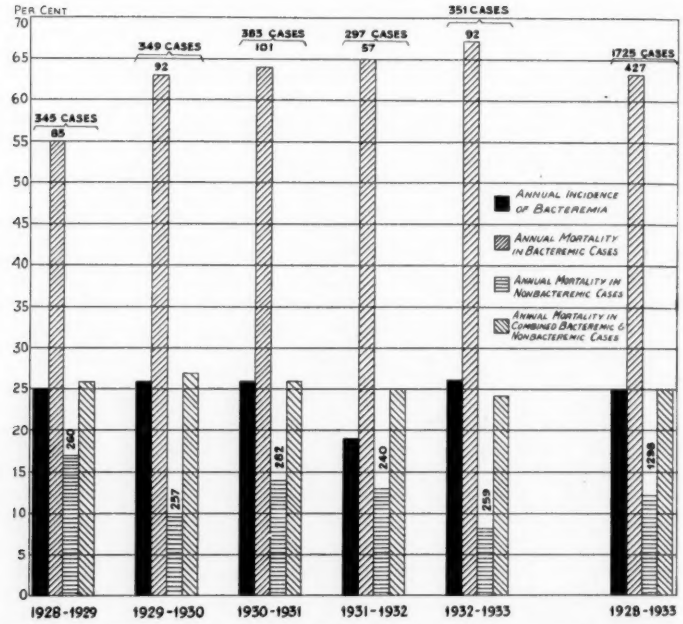

Chart 8.—The annual incidence of bacteremia and the annual mortality in 1,725 cases of pneumococcic pneumonia, due to a single type of pneumococcus, is shown, with the death rate in the bacteremic and in the nonbacteremic cases over a five year period and for each year separately.

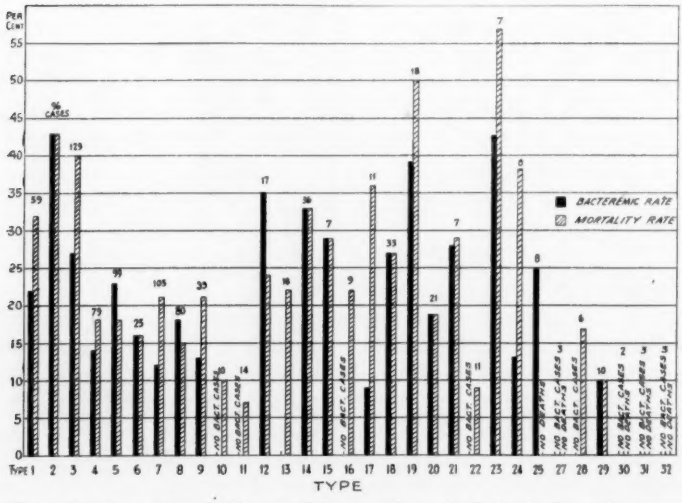

Chart 9.—Percentage incidence of bacteremia and of deaths in each pneumococcus type, from I to XXXII. The number of cases involved is given above each block. Only patients treated without specific serum are included.

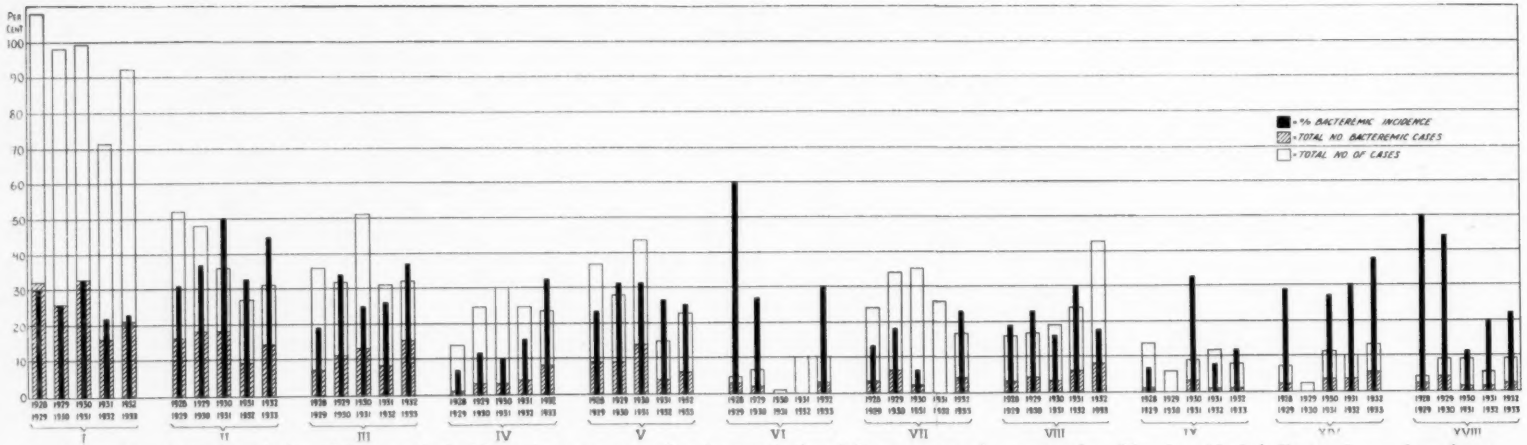

Chart 10.—Annual variation of bacteremic incidence in types occurring frequently in adult pneumococcic pneumonia. The clear block indicates the number of cases in each year; the superimposed cross-hatching indicates the number of cases of bacteremia; the black block indicates the bacteremic incidence per hundred cases, and the space between the horizontal lines denotes 10 cases and also 10 per cent.

MORTALITY RATE

In a recent article, Cecil and Plummer [4] called attention to the fact that in the case of type II the percentage of bacteremic incidence and the percentage of mortality approached each other. In our study of seventeen hundred and twenty-five cases of pneumococcic pneumonia of definite type due to a single pneumococcus, encountered during the last five years, it appeared that the bacteremic incidence and the rate of group fatality in pneumococcic pneumonias as a group were approxi-

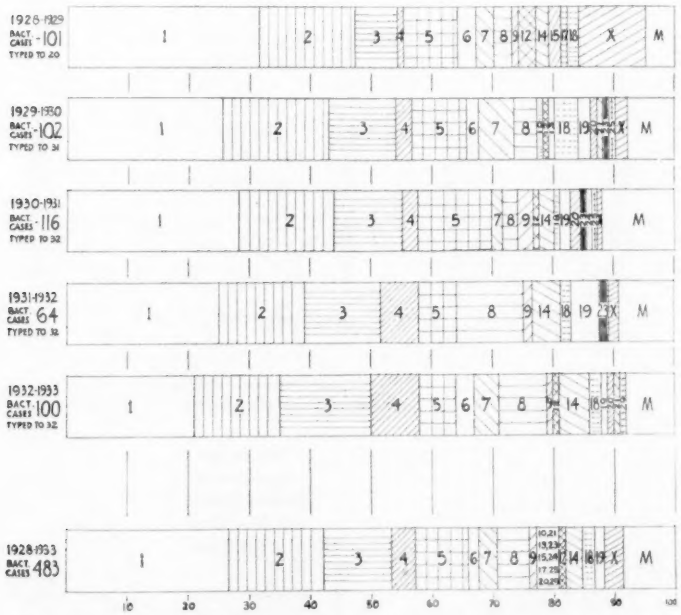

Chart 11.—Annual relative distribution of bacteremia according to each type of pneumococcus among 2,058 cases of pneumococcic pneumonia. *M* indicates a multiple infection.

mately the same (chart 8), i. e., 25 per cent, with the exception of one year (1931-1932) when the bacteremic incidence was lower than the mortality rate. In that year the bacteremic incidence was 18 per cent while the mortality rate was 25 per cent.

A glance at chart 8 will show, however, that from year to year there was a steady, though slight, increase in the mortality of bacteremic cases. This may be due to the increasing number of cases for which

4. Cecil, Russell L., and Plummer, Norman: Pneumococcus Type II Pneumonia, J. A. M. A. **98**:779 (March 15) 1932.

we have as yet no serum and, accordingly, no means of direct therapeutic attack.

The death rate in the bacteremic and in the nonbacteremic cases is very different, and is shown in chart 8. In general, the bacteremic mortality is two or more times greater than in the nonbacteremic cases.

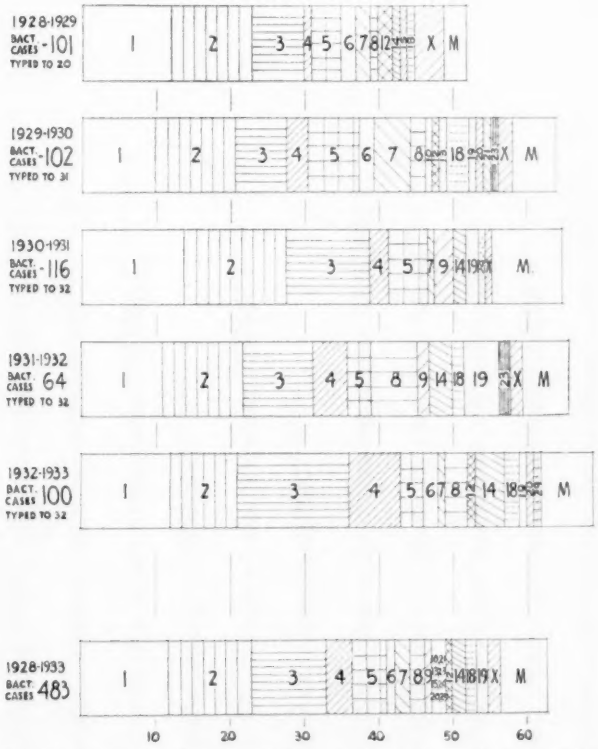

Chart 12.—Annual relative distribution of fatal cases of bacteremia due to various types of pneumococci among 2,058 cases of pneumococcic pneumonia. *M* indicates a multiple infection.

Patients infected with different pneumococcic types react so differently that it seemed well to study the mortality in the different types separately.

Interesting facts were revealed when the types we studied were separated with respect to their behavior as to bacteremia and mortality, as is done in chart 9. In many cases the percentage of bacteremia and mortality are the same, though the percentage of mortality ranges from 10 to 43. This is especially well shown in types II, VI, XIV, XV,

XVIII, XX, XXI and XXIX. On the other hand, in some instances, notably in type I, the bacteremic incidence is less than the mortality. This also occurs in types III, IV, VII, IX, XVII, XIX, XXIII and XXIV. There are other types in which the bacteremic incidence is greater than the fatality rate, as in types V, VIII and XII. There are some types, however, in which there were fatal cases but no bacteremia,

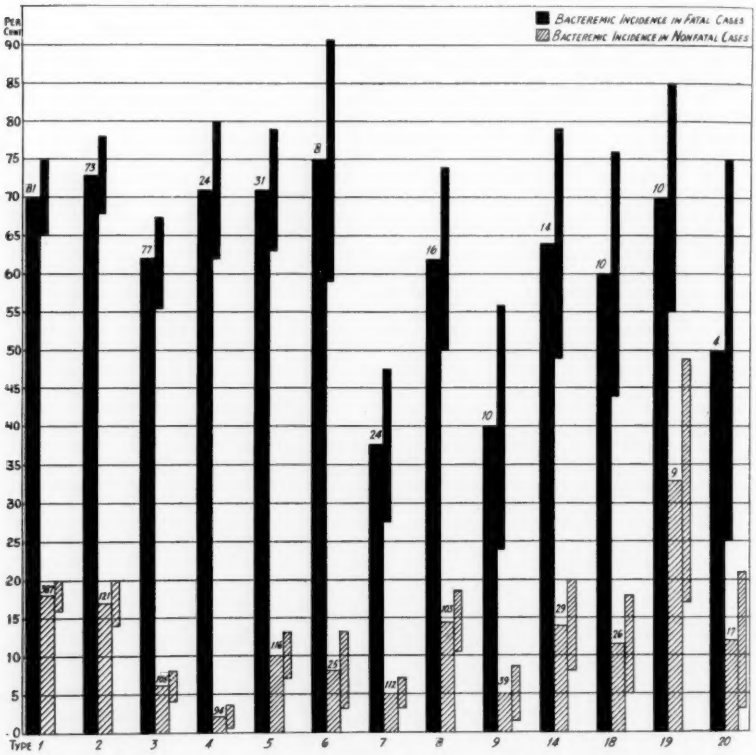

Chart 13.—Incidence of bacteremia in fatal (black) and nonfatal (cross-hatched) cases among thirteen of the most important types of pneumococcic pneumonia occurring in 1,725 cases due to a single type of organism. Note the relative infrequency of bacteremia in the nonfatal cases. The number of cases involved is given above each block. The bayonet indicates the standard error of the observation. Calculation of the standard error is indicated in the legend for figure 3.

as in X, XI, XVI, XXII and XXVIII, and there was one—type XXV—in which there was invasion of the blood in two of the eight cases, with recovery in all eight.

ANNUAL VARIATION IN BACTEREMIC INCIDENCE

In order to determine whether the incidence of bacteremia was constant or varied from year to year, a study of the annual incidence was made. In chart 10 the total bacteremic incidence for a number of frequent types is separated into the constituent years. The percentage of bacteremia is indicated against a cross-hatched block, which shows the number of cases in which the blood was invaded, and a clear block, which shows the number of cases during the year. The decline in the type I cases from year to year is striking. A decline occurred in the bacteremic cases with the exception of one year. The decrease in the percentage of bacteremia from 30 to 21 per cent in the last two years may have been brought about to a varying extent by: (1) the larger unitage of serum employed as probative serum, and (2) improvements in our typing practice, as well as (3) the introduction of typing from the lung juice, with consequent earlier treatment in some cases.

An increase seems to have occurred in the percentage of invasions of the blood among type II cases, though the total number of cases diminished. In type III, though the number of cases has been approximately the same in each year, there seems to be an upward trend in the bacteremia. In type IV the number of cases of bacteremia has steadily increased. In type V the percentage of cases of bacteremia at first increased and then decreased. Two bacteremic cases were observed in type VI in the first year of our study. In the second year they were fewer, and for two years there were no cases of invasion of the blood. Last year bacteremia occurred in four of the ten cases. In type VII the percentage of invasions of the blood increased and then diminished, though the number of cases diminished. One year there were no cases of invasions of the blood. The number of type VIII cases seems to be steadily increasing, and there is an increase in the percentage of bacteremia. In type IX there have been few cases, too few to study the trend. In type XIV the number of cases of bacteremia has increased, without significant changes in the number of cases. In type XVIII, though the cases have been few, the bacteremic incidence seems to have diminished.

No one can tell what studies such as these will reveal when they have been continued over a sufficient period. We may learn much of the epidemic variation of the different types. Possibly we shall learn to be forearmed with serum for approaching increased incidence, or with vaccine as a preventive to ward off needless illness and death. There may be cycles in these diseases caused by the different types, just as there are in scarlet fever and measles.

DISTRIBUTION OF BACTEREMIA AND FATALITIES

It seemed important to contrast the annual relative distribution of bacteremia and the deaths in bacteremic cases, with a view to determining whether there was marked variation in each type and from year to year. Accordingly, graphs 11 and 12 were prepared. Our study revealed that types I, II and III make up slightly more than 50 per cent of all the cases. Types I and II contribute between 30 and 40 per cent.

The importance and the variation of the other types is revealed. Type IV which, in the first year of our study, was responsible for only 2 per cent of the bacteremic cases, was responsible for 7.5 per cent in the last year. Type V became more important and then less. Type VIII gradually acquired greater importance. The number of multiple infections has varied from year to year. It was greatest (12 per cent) in the season of 1930-1931 when infection by Streptococcus haemolyticus was prevalent. The x group has disappeared as a cause of bacteremia in our series.

It is evident that type II, in spite of the separation of type V, has remained important as a cause of bacteremia, while type III has increased, though its relative importance as a cause of pneumonia, as shown in chart 1, has diminished.

On examining the relative distribution of deaths in the bacteremic cases for each type (chart 12), it will be found that in the bacteremic cases 64 per cent of the patients died, and that though 50 per cent of the bacteremic cases were caused by types I, II and III, only 33 per cent of the deaths were caused by the three types. This change from what was to be expected has been accomplished by the use of serum for types I and II.

Though the bacteremia in type II cases did not decline in incidence, the cases were relatively fewer. The portion of the death rate due to this type among the cases of bacteremia was diminished in the last year of our study, and the bacteremic fatality from this type became 8 per cent, whereas 12 or 13 per cent of the cases of bacteremia were due to this type.

The chart further reveals that an increasing percentage of the deaths in the bacteremic cases is due to the increasing number of deaths due to type III and the types of higher number described by Cooper. For these cases, serums or other direct treatment should be made available, if possible.

From what has already been said there can be no doubt that the occurrence of bacteremia is an event which exerts a marked influence on the outcome of pneumococcic pneumonia. We have accordingly shown in chart 13, thirteen of the most frequent types, and have indicated the bacteremic incidence in fatal and in nonfatal cases. Above

each block is placed the number of cases observed. We have indicated by the bayonet attached in each case the standard error of the specimen.

It is readily seen that the incidence of bacteremia in the fatal cases and in the nonfatal cases varies in the different types, and that invasion of the blood may be assigned less influence in producing death in some types than in others.

Types III and IV had a high bacteremic incidence among fatal cases and a relatively low one among those with recovery. Types VII and IX had a low bacteremic incidence in both fatal and nonfatal cases. In type XIX, both in fatal cases and in cases with recovery, there were frequent invasions of the blood stream.

SUMMARY

1. The incidence of bacteremia in connection with the fatality rate is listed for different types of pneumococcic pneumonia in a series of seventeen hundred and twenty-five cases due to a single type, occurring over a five year period, at Harlem Hospital.

2. The percentage of invasion of the blood differs for the different types, though in the main the percentages of invasiveness and mortality are approximately the same.

3. The importance of (1) differentiating the types formerly included as group IV or the x group and (2) of typing individual cases for prognosis and eventual treatment, when specific treatment is available, is manifest.

4. Only 3 per cent of pneumococcic pneumonias escape classification at the present time, when typing is carried from I to XXXII (Cooper).

5. The variation in percentage of invasion and fatality from year to year in different pneumococcic types is evidence of the variations which are encountered from season to season, and shows the necessity of extending over several years the testing of any proposed curative substance.

LEUKEMIC SINUS RETICULOSIS (MONOCYTIC LEUKEMIA) WITH INTESTINAL OBSTRUCTION

REPORT OF A CASE WITH PARTIAL AUTOPSY

ROBERT B. HAINING, M.D.
AND
THEODORE S. KIMBALL, M.D.
LOS ANGELES
AND
OSMONDE W. JANES, M.D.
GLENDALE, CALIF.

Thirty years ago acute leukemia was regarded as a disease of but one type—lymphatic leukemia. Gradually myelogenous acute leukemia came to be recognized, which seems to occur far more frequently than the lymphatic variety. Today room is being made for a third claimant —monocytic leukemia.

Full acceptance of monocytic leukemia as a clinical and pathologic entity will depend ultimately on indisputable proof of the derivation of the circulating monocytes. Such proof will involve the recognition of a third hematopoietic system, the occasional hyperplasia of which may logically be expected to result in leukemia comparable to myeloid and lymphoid leukemia. Unfortunately, the ancestry of cells, like the ancestry of human beings, is often easy and pleasing to claim but hard to verify. The studies of Maximow,[1] of Kiyono [2] and of Sabin [3] have convinced most investigators that circulating monocytes are derived from some part of the reticulo-endothelial system. Exactly which part and the precise nature of this system are still somewhat obscure.

The first case of monocytic leukemia was reported by Reschad and Schilling-Torgau [4] in 1913. In the subsequent twenty years the new-

From the Department of Pathology, Los Angeles County Hospital; the Division of Medicine, College of Medical Evangelists, and the Glendale Sanitarium and Hospital.

1. Maximow, A.: Les relations des cellules sanguines avec le tissu conjonctif et avec l'endothélium, Ann. d'anat. path. **4**:701 (July) 1927.

2. Kiyono, K., and Nakanoin, T.: Weitere Untersuchungen über die Histiozyten, Acta scholae med. univ. imp. in Kioto **3**:55, 1919.

3. Sabin, F. R.: Studies on Living Human Blood Cells, Bull. Johns Hopkins Hosp. **34**:277, 1923. Sabin, F.; Doan, C. A., and Cunningham, R. S.: Discrimination of Two Types of Phagocytic Cells in the Connective Tissues by the Supravital Technique, Contrib. Embryol. **16**:125, 1925.

4. Reschad, H., and Schilling-Torgau, V.: Ueber eine neue Leukämie durch echte Uebergangsformen (Splenozytenleukämie) und ihre Bedeutung für die Selbständigkeit dieser Zellen, München. med. Wchnschr. **60**:1981, 1913.

comer to the leukemic field has sometimes been hard put to it for survival. The first few reported cases were dismissed by certain writers as instances of "an ordinary myelogenous leukemia with a one-sided differentiation into monocytes" (Hirschfeld,[5] 1925) or a "temporary variant of myelogenous leukemia" (Naegeli,[6] 1923). In 1927 Piney[7] declared that monocytic leukemia belonged to the group of myeloses, "not being a special form of leucosis (leukemia) dependent upon proliferation of the cells of a third hematopoietic system." However, in 1928 Merklen and Wolf[8] seemed to draw conclusive distinctions for the three types of leukemia, and in 1930 Dameshek[9] assembled eighteen well substantiated cases of acute monocytic leukemia. Recently, Foord, Parsons and Butt[10] (the last two workers being from the laboratory of the Los Angeles County Hospital) compiled an excellent review of the literature and added four cases (two with autopsy and one with biopsy).

RETICULO-ENDOTHELIAL SYSTEM

All attempts to define the origin of the phagocytic group of cells, or even to classify the phagocytes as they arrange themselves in various diseases, have been unsatisfactory, and the results probably will require modification as the information becomes more exact. Aschoff seemed to illumine the darkness when he dignified these scattered cells by regarding them collectively as a single organ which he named the reticulo-endothelial system. However, MacCallum[11] expressed the opinion that "Aschoff has cut the knot by merely coining a name—the reticulo-endothelial system—which evades any hard and fast adherence to a theory of origin of the cells since both reticulum cells and endothelium are brought in." MacCallum maintained that the endothelial cells which form the lining of the blood and lymph channels have the one function of lining these channels, and that one indulges one's fancy when one supposes that they ever act as phagocytes or that they divide to form

5. Hirschfeld, H.: Handbuch der Krankheiten des Blutes und der blutbildenden Organe, Berlin, Julius Springer, 1925, vol. 1, p. 411.

6. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, ed. 4, Berlin, Julius Springer, 1923.

7. Piney, A.: Recent Advances in Hematology, Philadelphia, P. Blakiston's Son & Co., 1927, p. 47.

8. Merklen, M., and Wolf, M.: Leucémies à monocytes, Rev. de méd., Paris **45**:154, 1928.

9. Dameshek, W.: Acute Monocytic (Histiocytic) Leukemia, Arch. Int. Med. **46**:718 (Oct.) 1930.

10. Foord, A. G.; Parsons, L., and Butt, E. M.: Leukemic Reticulo-Endotheliosis (Monocytic Leukemia), J. A. M. A. **101**:1859 (Dec. 9) 1933.

11. MacCallum, W. G.: Text-Book of Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1932.

wandering cells of any sort. Maximow [12] shared MacCallum's distaste for the term "reticulo-endothelium" as applied to the system of active phagocytic wandering cells. He thought that "the most appropriate name for these cells is histiocytes. Another widely used name, reticulo-endothelium, is not suitable; first, because it refers to only one of the representatives of the system, namely, to the reticular cells, and secondly because it creates the incorrect impression that the endothelium of the common blood vessels also belongs to this system."

The confusion undoubtedly arises from the old difficulty of finding a name the implications of which are restricted to the ascertained facts. The cellular elements in the liver, the spleen, the lymphoid tissues, the bone marrow, the connective tissue, the blood and some of the glands of internal secretion were recognized and grouped into a "system" because of the common ability to store dyes. Phagocytosis is the essential property of the reticulo-endothelial system, and it was on the basis of this common function that the reticulo-endothelial system was described and defined by Aschoff. Unfortunately, the name he gave it has exercised a tyranny on the minds of subsequent writers, some of whom have incautiously assumed that the cells of the reticulo-endothelial system are identical anatomically and genetically as well as functionally. These assumptions rest on uncertain ground. If Aschoff's term is used, it should be remembered that the knowledge of the reticulo-endothelial system is still largely confined to the functional phenomena which he described. The origin and interrelationships of the scavenger cells are not fully understood.

For the sake of formulating some simple concepts of the subject it may be pardonable to mix fact with theory. The "reticulo-endothelial cell" is distinguished chiefly by its powers of phagocytosis, of locomotion and of alteration in size and in activity, in all of which properties it somewhat resembles the ameba. Apparently it may be mobilized by the functional demand, either locally or from many widely separated sources. One sees it at work in the most active form as a macrophage in inflammatory processes. When it is not active it is found at rest chiefly in three locations: (1) in the sinuses of the spleen, the lymph glands, the liver and the bone marrow; (2) in the connective tissues (histiocytes), and (3) in the blood (monocytes). Changes from one type of cell to another have been reported, but there seems irrefutable evidence for only one transformation: The lymphocyte may apparently develop into an active monocyte or into a histiocyte, which in turn may become an inactive fibroblast.

---

12. Maximow, A., and Bloom, W.: Text-Book of Histology, Philadelphia, W. B. Saunders Company, 1930, p. 126.

THE MONOCYTE

Some authorities maintain that in the adult there are primitive reticular or reticulo-endothelial cells which can develop in any one of three or four directions depending on the stimulus which the cell receives. Of course, if this process becomes irreversible late in the development of the cell, transformations between the less differentiated types of cells seem theoretically possible. However, as has been seen, there is convincing evidence for but one such transformation (from lymphocyte to monocyte, Maximow and Bloom [12]). Members of the triphyletic or polyphyletic school seem to base their opinion on firmer ground. They assume (in harmony with the monophyletists) a common ancestral cell for all of the leukocytes. They think, however, that at the time of birth these ancestral cells have already been differentiated (probably irreversibly) into hematopoietic tissues, each tissue capable of producing its own specific leukocytic cell (lymphocyte, monocyte or granulocyte).

Amid the conflicting views it seems that the weight of evidence supports the theory of a sharp separation between the monocyte on the one hand and the granulocyte and the lymphocyte on the other. The evidence also indicates an independent origin for monocytic tissue, probably in some part of the reticulo-endothelium.

Gittins and Hawksley [13] in a recent communication suggested that the site of origin of the monocytes may be the lymphatic endothelium. They pointed out that, according to Maximow, lymphocytes are produced not from the lymphatic endothelium but predominantly from older lymphocytes, so that what is seen in lymphatic leukemia is not an endothelial proliferation but an excessive multiplication of formed lymphocytes in the lymph glands. "This granted, it is not surprising that lymphatic endothelial proliferation per se produces not increased numbers of lymphocytes but histiocytes."

A conception similar to that of Gittins and Hawksley was put forward by Joan Ross,[14] who emphasized the difference between endothelium (the lining of the ordinary blood and lymph channels) and "sinus reticulum" or "littoral" cells, the cells lining the sinuses of the spleen, the bone marrow, the lymph nodes and so on. Of course, this may be merely another way of designating the conception of reticulo-endothelial endothelium, but perhaps it is important to use a term

13. Gittins, R., and Hawksley, J. C.: Reticulo-Endotheliomatosis, Ovarian Endothelioma and Monocytic (Histiocytic) Leukemia, J. Path. & Bact. **36**:115 (Jan.) 1933.

14. Ross, J. M.: The Pathology of the Reticular Tissue Illustrated by Two Cases of Reticulosis with Splenomegaly and a Case of Lymphadenoma, J. Path. & Bact. **37**:311 (Sept.) 1933.

which automatically creates a distinction between the endothelium of the common blood vessels and the cells lining the sinuses of the spleen, liver, lymph nodes and bone marrow. The accompanying diagram (fig. 1) is an attempt to represent the development of the leukocytes as conceived by Ross.

The truth is, of course, that the problem is still seen "through a glass darkly." With all of the improved technical methods of study, one cannot clearly trace the origin and interrelationships of the important group of cells which have been variously termed large mononuclear cells, macrophages, polyblasts, endothelial leukocytes, histiocytes, clasmatocytes, adventitial cells, reticulo-endothelial cells and monocytes. But in spite of the hiatuses in the knowledge of these cells, there is a mounting tendency to postulate the existence of a third hematopoietic

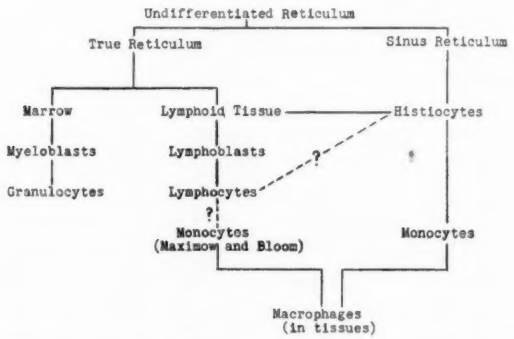

Fig. 1.—Diagram showing the development of the leukocytes as conceived by Ross.[14]

(monocytopoietic) system which is closely related to what is known as the reticulo-endothelial system, the proliferation of which may give rise to characteristic changes in the blood and in certain other tissues which are recognized as monocytic leukemia, as leukemic reticuloendotheliosis or as leukemic sinus reticulosis (Ross' term).

CLASSIFICATION AND TERMINOLOGY

Systematic classifications of the hyperplasias of the blood-forming organs have followed many vogues. Most of the investigators have erected their schemes on Aschoff's conception of the reticulo-endothelial system. Foord, Parsons and Butt[10] recently advanced a modified classification of this kind. Ross[14] expressed the opinion that such an approach does not allow sufficiently for the developmental possibilities of the cells of the stroma (reticular cells) of the hematopoietic organs. She proposed a classification based on Maximow's theory of the multi-

potential capacity of the reticulum for differentiation. Her tabulation, slightly abbreviated, follows:

I. Without Disturbance in Metabolism [15]

A. True Reticuloses

Hyperplasia affecting undifferentiated cells with unrestricted potency for differentiation; i. e., follicular reticulum of lymph glands, malpighian bodies of spleen and undifferentiated reticulum cells of connective tissue

1. Lymphoid
2. Fibrillary
3. Histiocyte
4. Myeloid
5. Giant cell
6. Fibrillary plus giant cell
7. Unrestricted differentiation of cells (lymphadenoma)

B. Sinus Reticuloses

Hyperplasia affecting cells already specialized; i. e., sinus reticulum (littoral cells)

1. Leukemic (monocytic leukemia)
2. Aleukemic

II. With Alteration in Metabolism

Hyperplasias of reticulum cells with differentiation to histiocytes which store various substances (usually lipoids)

A. Storage histiocytoses
B. Lipoid histiocytoses
C. Lipoidoses

(Gaucher's disease; Christian's syndrome; xanthomatosis; Niemann-Pick's disease; hypercholesterolemic splenomegaly)

It will be seen at once that this classification assumes, in harmony with Maximow's theories, that the venous sinuses of the spleen and bone marrow and the lymph sinuses of the spleen and lymph glands are lined by differentiated reticular cells. These cells are similar to the Kupffer cells of the liver. Like the Kupffer cells, these reticular cells are phagocytic, and they are probably entirely different from the endothelial cells lining ordinary blood and lymph channels. To call both groups of cells "endothelial" is confusing. The cells of the sinus reticulum have been aptly termed littoral (seashore) cells (Siegmund,[16] 1925). The use of such a term may tend to discredit the popular conception that all blood and lymph channels are lined by the same kind of "endothelium."

As early as 1924, Letterer [17] suggested that a distinction should be drawn between reticulum and reticulo-endothelium (sinus reticulum)

15. "In group I localized tumour formation might be expected in some cases" (Ross [14]).

16. Siegmund, H.: Verhandl. d. deutsch. path. Gesellsch. **20**:260, 1925; quoted by Ross.[14]

17. Letterer, E.: Aleukämische Retikulose, Frankfurt. Ztschr. f. Path. **30**:377, 1924.

in the classification of the systemic diseases of the reticulo-endothelial system. We have mentioned MacCallum's [11] objection to the term reticulo-endothelium on the ground of its evasiveness. The term groups together two tissues which, though related, are better kept in mind as distinct because they perform different functions and probably (as Ross suggested) respond independently to pathogenic factors. Sinus reticulum is chiefly involved in the reaction to pigments and dusts, in Addison's disease, in syphilis and in typhoid. The true reticulum of the follicles is involved in cases in which the lymph glands drain a pyogenic infection and in glandular fever (Pratt,[18] 1931). Ross assumed this reactive specificity to be true of the hyperplasias of the reticulum of the blood-forming organs, and her classification emphasizes this theory.

If Ross' conclusions are accepted, the sinus reticulum is to be regarded as the third hematopoietic system, and monocytic leukemia is extricated from the too large group of reticulo-endothelioses to become known as leukemic sinus reticulosis. This term is descriptive and distinctive; it represents the best approximation to the real nature of the condition which the present knowledge permits.

LEUKEMIA

Nature of Leukemia.—In spite of certain obvious resemblances to an inflammatory condition (such as the presence of fever, leukocytosis and so on) there are good grounds for regarding leukemia as a malignant neoplastic process. In his recent series of Colver lectures delivered at the College of Medical Evangelists, Dr. William Boyd [19] proposed that the generic term leukemia should not be allowed to lead workers to the supposition that the members of the group of the leukemias are intimately related or that other conditions cannot be closely related simply because they do not exhibit similar hematologic phenomena. Probably lymphoid leukemia has a more fundamental resemblance to lymphosarcoma than it has to myeloid or monocytic leukemia or to erythremia. The evidence for this probability is strengthened by the work of Furth, Seibold and Rathbone,[20] who studied experimentally produced lymphomatoses (lymphatic neoplasms with or without leukemia) in mice. They concluded:

> Leukemic lymphomatosis (lymphoid leukemia), aleukemic lymphomatosis, lymphosarcoma, and leukosarcoma are malignant processes; they are different manifestations of the same disease. . . . Leukemic lymphocytes are not lymphoblasts but malignant (pathological) lymphocytes with limited power of maturation,

18. Pratt, C. L. G.: Pathology of Glandular Fever, Lancet **2**:794 (Oct. 10) 1931.

19. Boyd, W.: Lectures to be published.

20. Furth, J.; Seibold, H. R., and Rathbone, R. R.: Experimental Studies on Lymphomatosis of Mice, Am. J. Cancer **19**:521 (Nov.) 1933.

and when these cells multiply, their characteristics persist. These characters determine their ability to produce tumors, to invade the blood stream, to transmit the disease to related or unrelated mice, to localize in certain organs, etc. The essential change in leukemia consists not in the appearance of immature blood cells in the circulation (analogous to the "shift to the left" of Arneth), but in invasion of the blood stream by malignant lymphocytes.

Gittins and Hawksley [13] recently reported a case of "reticulo-endotheliomatosis, ovarian endothelioma, and monocytic (histiocytic) leukemia." They regarded their case as evidence in favor of the essentially neoplastic nature of monocytic leukemia, though they remarked that "considering the mesenchymal origin of endotheliomata and sarcomata on the one hand and blood cells on the other, lack of clinical association between the two is surprising."

If the theory is accepted that the essential process in any type of leukemia is a malignant neoplasia of the particular hematopoietic tissue with the invasion of the blood stream by characteristic malignant cells, one must admit that the most disturbing fact opposing the theory is the infrequency of specific focalization. Malignancy and neoplasia are closely associated in the minds of investigators with infiltration and with localized tumor formation. However, this association may not be as close as has been supposed. Even if the relation is essential, one may support the theory of malignant neoplasia by pointing to the well recognized occurrence of leukemia with chloroma and with lymphosarcoma, to the occurrence of myeloma in myeloid leukemia (true myeloid myeloma has been described; MacCallum [11]) and to the occurrence of the tumor in monocytic leukemia described by Gittins and Hawksley [13] which is similar to the lesion in the present study.

Perhaps it is time that the leukemic phase of the permanent hyperplasia of the blood-forming organs be regarded as of great diagnostic significance but of small pathologic importance. The malignant neoplasm seems the essential process (certainly no other word than "malignant" could imply the inexorable mortality of 100 per cent); the leukemia seems more or less incidental. In other words, leukemia is not a disease of the blood nor, indeed, a disease at all; it is probably the reflection in the blood stream of a hidden malignant change affecting the hematopoietic cells of a fixed line of development (myeloid, lymphoid or sinus reticulum). Sometimes evidence of this neoplasia may be seen in the form of tumor growth. In this communication an arresting example of such a tumor is described which occurred in a case of leukemic sinus reticulosis (monocytic leukemia).

CLINICAL FEATURES

We have stated that the most enlightening pathologic name for permanent hyperplasia of the monocyte-producing tissue is leukemic

sinus reticulosis. Clinically, however, there is considerable justification for the older name—monocytic leukemia. The morphologic recognition of immature (probably malignant) monocytes in the blood is still the single pathognomonic means of antemortem diagnosis. There are no other clinical characteristics of the disease which may be relied on to differentiate monocytic leukemia from the other leukemias.[21] Therefore, the term monocytic leukemia serves a useful clinical purpose in stressing the one practicable diagnostic procedure.

The onset is usually gradual, with inexplicable fatigue, though it may be acute. Some degree of fever is almost constant; in the acute cases, the temperature may be high. At some stage in the process, gingivitis is nearly always present. The gums swell; they often ulcerate and bleed. Adenopathy is variable. Theoretically, slight enlargement of the spleen and of the liver should be present and has been noted in most of the recorded cases, but, in our opinion, the ability to detect slight enlargements of the liver and of the spleen varies too much with the individual examiner to be of great value. Petechiae and purpuric manifestations frequently occur. The duration of the disease is from two to thirty weeks, with an average of ten weeks (Dameshek[9]).

Microscopic examination of the blood usually reveals secondary anemia and monocytic leukocytosis (though aleukemic cases have been reported, for example, that of Letterer[17]). The total white cell count has been found to range from 2,000 (Wyschegorodzowa[22]) to 416,000 (Swirtschewskaja[23]), but the count tends to be lower than that of the other two leukemias.

The differential count of the white cells usually shows that from 50 to 75 per cent are of the monocyte type. It is usually stated that the monocytes in monocytic leukemia are of two varieties: (1) the monocyte of the normal blood and (2) a more immature cell, the histiocyte, assumed to be the forerunner of the monocyte (Dameshek). It is just as probable that the second type of cell is not the ordinary histiocyte (reticulo-endothelial cell, active or resting wandering cell or

21. Since this manuscript was prepared for publication an article has appeared by Claude E. Forkner (Clinical and Pathologic Differentiation of the Acute Leukemias, Arch. Int. Med. **53**:1 [Jan.] 1934). This writer expressed the belief that it is often possible to distinguish clinically the three main types of acute leukemia. He thinks that the diffuse swelling of the mucous membranes, particularly of the gingivae, usually accompanied by ulceration and necrosis, is characteristic of acute monocytic leukemia.

22. Wyschegorodzowa, W. D.: Sur Frage der monozytären Leukämie, Folia haemat. **28**:355 (July) 1929.

23. Swirtschewskaja, B.: Leukemic Reticulo-Endotheliosis (Monocytic Leukemia): A Disease of the Reticulo-Endothelial System, Virchows Arch. f. path. Anat. **267**:456, 1928.

clasmatocyte) but a cell produced by rapid, disorderly proliferation (a malignant process) of the sinus reticulum, the assumed site of origin of the monocyte.

The all-important diagnostic point is the accurate recognition of the monocyte, and this usually is not difficult. Monocytic cells are larger than other normal blood cells (in dry smears the diameter may be from 30 to 40 microns). The protoplasm is far more abundant than that of lymphocytes, so that the nuclei are relatively smaller. The nuclei are oval or kidney-shaped, and there is a tendency to horseshoe configuration in the older forms. When the Wright or the Giemsa stain is used, the cytoplasm has a typical ground glass appearance and is blue-gray. Azure granules, when present, are massed around the nucleus, leaving a nongranular periphery. The chromatin of the nucleus is spun into a fine meshwork (coarser in the older cells) which creates an appearance of homogeneity. The color of the nucleus is violet. Pseudopodia are often seen. In moist preparations the monocytes evince marked motility, and if they are stained supravitally, active ingestion of dyes may be observed. The Wright or the Giemsa stain alone is sufficient to identify the cells in a clearcut case, but sometimes the oxidase reaction helps to differentiate monocytes from lymphocytes and from myelocytes. (Monocytes usually give a negative oxidase reaction. If they give a positive oxidase reaction, the granules are small and infrequent.)

Beside the other types of acute leukemia, agranulocytosis and acute infections with accompanying monocytosis may have to be differentiated. The appearance of large numbers of immature monocytes (histiocytes or malignant (?) monocytes) and the progressive course to a fatal termination readily exclude the diagnosis of benign monocytosis. Agranulocytosis (malignant neutropenia) as a rule results in complete disappearance of the granulocytes; this condition is never seen in monocytic leukemia.

HISTOLOGY

Collections of large mononuclear cells resembling the monocytes of the blood are found in the lymph nodes, the spleen, the periportal spaces of the liver, the kidneys, the bone marrow and the reticular perivascular stroma of practically all of the organs. In the spleen and in the lymph nodes this proliferation and infiltration are so marked as to efface the normal architecture. Slight myeloid hyperplasia, especially in the spleen, has been noted by a few observers. Ross [14] expressed the opinion that some of the reported cases are carefully enough described from a histologic point of view as to make it possible to state that the process affected particularly the littoral cells (cells of the sinus reticulum). The substantiation of her theory that specific factors produce specific involve-

ment of the "true" reticulum in some cases and of the sinus reticulum in others requires more accurate histologic investigation than has been made in most of the reported cases.

MONOCYTIC LEUKEMIA WITH INTESTINAL OBSTRUCTION

We are not recording such a rare incidental lesion as intestinal obstruction in order to suggest a new sign characteristic of monocytic leukemia. Gastro-intestinal complications are not particularly characteristic of any of the leukemias. So far as is known, the only other example of intestinal obstruction recorded as bearing a causal relation to a disease possibly related to leukemia is that of amyloidosis of the intestines occurring in a case of multiple myeloma (Randall[24]). Of course, this lesion is probably by no means peculiar to multiple myeloma and is just as likely to occur in any wasting disease of long standing.

The only other report, to our knowledge, of actual tumor formation in monocytic leukemia is a case described by Gittins and Hawksley.[13] A 1 year old child presented the typical blood picture of monocytic leukemia, diffuse reticulosis (so-called reticulo-endotheliosis) and bilateral ovarian tumors, each of which weighed 210 Gm. The tumors were composed chiefly of cells identical with those observed in the other tissues. These lesions seem exactly comparable to the intestinal tumor which we are describing. The two cases constitute evidence against the theory of infectious etiology. They argue in favor of the theory that monocytic leukemia is a neoplastic process. In terms of Ross' classification, they must represent either (1) a combination of true reticulosis (of the connective tissue reticulum of the rectal wall and of the ovaries) and of sinus reticulosis (monocytic leukemia) or (2) leukemic sinus reticulosis with metastatic blastomatous growths simulating those seen in chloroma.

REPORT OF CASE

History.—Mrs. A., a white woman, aged 34, was admitted to the Glendale Sanitarium and Hospital on June 8, 1932. She was in active labor and eight hours after admission was delivered of a normal girl, weighing 5 pounds and 7 ounces (2,466.4 Gm.). Numerous rectal examinations at this time revealed nothing abnormal. Unfortunately, no study of the blood was made. Repeated examinations of the urine revealed nothing significant. The mother and child were discharged on June 18, each in good condition; the mother passed through the puerperium uneventfully.

On June 2, 1933, almost one year from the date of the previous admission, the patient was admitted to the hospital complaining of abdominal pain with distention and obstipation. The past history revealed that she had had influenza, frequent

24. Randall, O. S.: Multiple Myeloma Complicated by Intestinal Obstruction Due to Amyloid Infiltration of the Small Intestine, Am. J. Cancer **19**:838 (Dec.) 1933.

colds and the "usual childhood diseases." The only child was well. One abortion, in 1922, was self-induced. Her husband and both of her parents were living and in good health.

She thought that the present illness began in the latter part of January 1933, when she began to feel tired and listless and suffered attacks of "light-headedness." About this time she noticed constipation, which gradually grew worse. She remembered no purpuric manifestations or bleeding from the gums.

On May 28 she observed that the abdomen was distended. It was almost impossible to obtain a bowel movement, even with the aid of cathartics. On May 30 she took a bottle of magnesium citrate; on May 31, Ex-Lax, and on June 1, castor oil and a glycerin and turpentine enema, with no results. The abdominal distention became marked, and when abdominal pain ensued she came to the hospital.

Physical Examination.—The physical examination on June 2 revealed a slightly pale, dyspneic, fairly well nourished woman. The temperature was 99 F. (37.2 C.), the pulse rate, 72, the respiratory rate, 20, and the blood pressure, 136 systolic and 90 diastolic. The abdomen was extremely distended, so that no accurate palpation could be performed. The teeth and gums showed good hygienic care; there was no evidence of bleeding. No ophthalmoscopic examination was made of the eyes. The breath sounds were normal, dyspnea apparently being due to the abdominal distention. The heart was not shown to be enlarged on percussion; there were no murmurs or arrhythmia.

Rectal examination revealed a constricting mass located about 3 inches (7.62 cm.) from the anus. The mass was firm and surprisingly smooth, and it was impossible to pass the finger beyond it. On proctoscopic examination the mucosa covering the mass was seen to be flecked with a few small bleeding points. There was no ulceration.

Bimanual examination was difficult because of the distention, but the uterus was found to be apparently normal in size and slightly retroverted. Both of the adnexal areas seemed tender.

A diagnosis was made of intestinal obstruction due to carcinoma of the rectum, though a rapid frozen section of a piece of tissue from the region of the mass was reported by the pathologist, Dr. O. B. Pratt, as "showing the mucosa of the bowel to be without evidence of malignancy."

Chemical examination of the blood revealed: nonprotein nitrogen, 34.2 mg. per hundred cubic centimeters, and chlorides, 420 mg. The results of the Wassermann test were negative.

Course.—On June 2, 1933, a left inguinal colostomy was performed by Dr. G. K. Abbott, who reported the finding of a hard dense mass with a diameter of 1¼ inches (3.18 cm.) in the anterior rectal wall which was adherent to the lower segment of the uterus and could not be moved. The surface of the mass on the rectal side was smooth. In the pelvis were palpated other nodules surrounding the rectum and behind the fundus of the uterus.

The patient seemed to improve following the colostomy, and considerable fecal material was expelled through the colostomy tube.

On June 6 the colostomy tube was removed, and a soft diet was prescribed. On June 9 the patient began to vomit and appeared toxic. The condition grew progressively worse in spite of repeated colonic irrigations. On June 13 she complained of severe abdominal pain. The abdomen was distended and silent. She was taken to the operating room and catheter drainage of two loops of the small intestine was performed by reopening the recent abdominal incision. On June 14 the patient died.

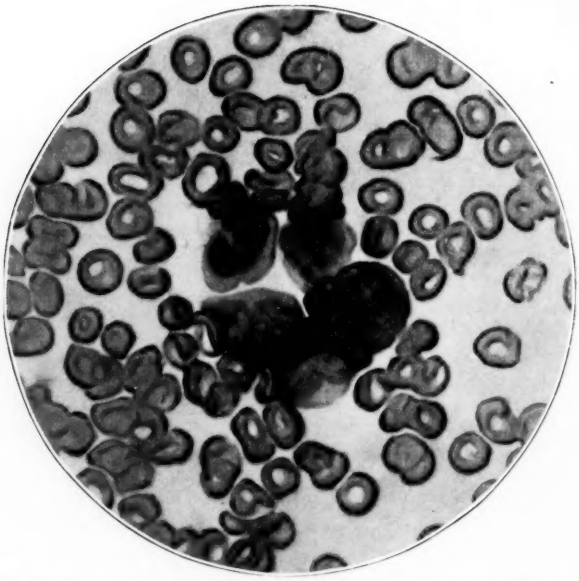

Fig. 2.—Photograph of a blood smear showing characteristic cells; × 900.

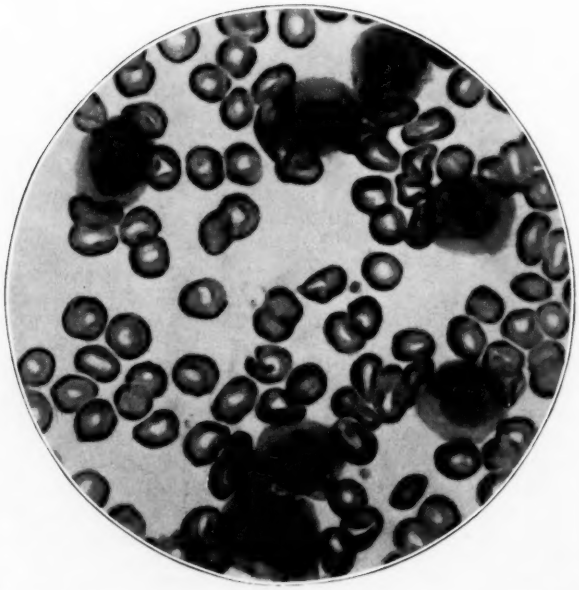

Fig. 3.—Photograph of a blood smear showing characteristic cells; × 900.

Autopsy.—Consent was obtained for a partial autopsy, which was performed by reopening the operative incision (Dr. Janes). The uterus was slightly enlarged and symmetrical, and its posterior surface was densely adherent to a hard mass in the rectum. The wall of the rectum at this level was infiltrated and thickened. It measured about 2 cm. in cross-section and almost completely obliterated the lumen of the bowel at this point. The fallopian tubes and the ovaries were normal in macroscopic appearance. The liver was smooth and presented no gross abnormalities. The spleen was moderately enlarged.

Consent was not obtained for the complete removal of any of the organs; neither was it possible to secure specimens of the bone marrow. However, blocks from the uterus, tubes, ovaries, rectum and spleen were saved for histologic examination. Sections of these tissues, with the blood smears were studied at the Los Angeles County Hospital by Dr. T. S. Kimball (assistant pathologist) and by Dr. R. B. Haining (resident in pathology). Their opinions were corroborated by Dr. Newton Evans (chief pathologist); Dr. O. B. Pratt and Dr. Verne R. Mason (Los Angeles), and Dr. Alvin G. Foord (Pasadena).

Hemogram.—Several unstained smears made from the patient's blood on June 13, 1933, were submitted. The leukocytes in all of the smears were carefully studied (Dr. Kimball), and in each case the monocytes were found to form from 75 to 90 per cent of the total leukocytes. The following differential count represents the average of several counts: polymorphonuclear neutrophils, 2 per cent; basophils, 1.5 per cent; eosinophils, 0; lymphocytes, 11 per cent; myelocytes, 0; myeloblasts, 0; mature monocytes, 36 per cent; immature monocytes, 49 per cent, and unclassified cells, 0.

Microscopic Examination.—Rectal Wall: Examination with a hand lens showed the usual muscular wall with a well defined dark streak running lengthwise through the midportion of the muscle. The submucosa and the mucosa were replaced by a solid mass of tissue which took a darker stain than did the muscle fibers. This mass was homogeneous except for one round area 5 mm. in diameter 1 cm. from the muscular wall. Examination with a low power lens showed the dark streak in the muscular wall to be a zone of closely packed, fairly round cells which in some areas were perivascular but in others appeared to bear no relation to the vascular channels. From this band of cells there were many smaller extensions at right angles into the muscle bundles, giving the effect of a tree with many stubby branches. The smaller accumulations of cells were almost always associated with small blood vessels. A similar collection of cells was noted on the serous surface associated with the small blood vessels. The most striking feature, however, was the appearance of the mass of tissue which replaced the inner coats of the rectum. It was composed almost entirely of closely packed cells with little fibrous reticulum. Several fairly large blood vessels were present in this tumor, but the cellular collection was massive and no association with blood vessels could be demonstrated. The small round area seen with the hand lens appeared to be lymphoid tissue. Examination of the cellular detail by the oil-immersion and the high dry lens showed several interesting and, we believe, diagnostic facts. The cells were considerably larger than those seen in the usual case of myelosis or lymphadenosis with infiltration of tissue. The cytoplasm of each cell was more abundant than is seen in myelocytes or in myeloblasts and stained light pink with no demonstrable granules. The nuclei almost without exception showed notching or lobulation. There was a definite nuclear membrane with a few fine strands of chromatin throughout the nucleus, but with no large

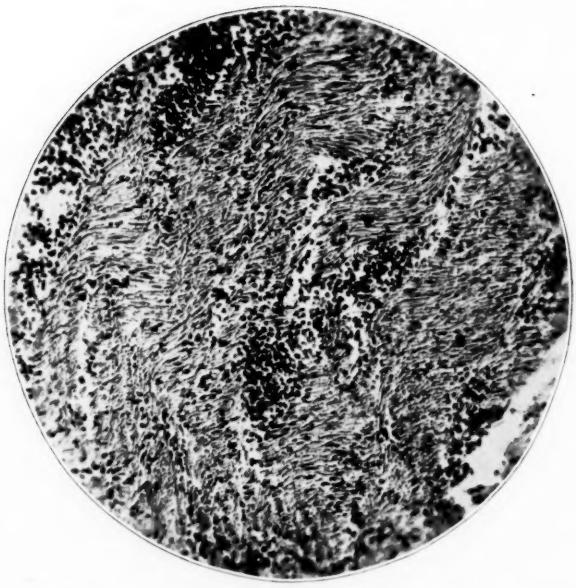

Fig. 4.—Photograph of a section from the rectal wall showing the marked cellular infiltration; × 120.

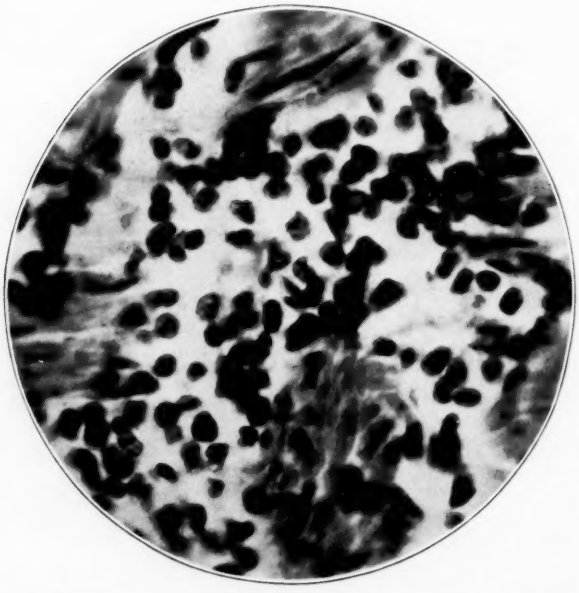

Fig. 5.—Photograph of tissue from the rectal wall showing greater cellular detail than figure 3; × 500.

clumps. Nucleoli were conspicuously absent from the great majority of the cells. On the other hand, mitoses were numerous, showing great activity in the growth of the cells. The presence of so many mitotic figures suggests either development of the cells in situ or an infiltration of cells from the blood. If the latter view is correct, the cells were autonomous and had neoplastic faculties. A small percentage of smaller cells containing eosinophilic granules were present. No evidence could be observed that the endothelial cells within the blood vessels were actively growing and producing the typical cell. A fine hyaline reticulum appeared between nearly all of the cells, and a stain for reticulum showed a delicate reticular tissue pervading the entire mass with individual fibers around nearly every cell or, at the most, around each two or three cells. On comparing the structure of the small island of lymphoid tissue with that of the main tumor, a striking difference

Fig. 6.—Photograph of tissue from the ovary showing cellular infiltration; × 120.

was noted. In the lymphoid tissue only a small number of fibers was observed, all being uniform in size and in distribution.

Spleen: The normal architecture was markedly altered, so that only an occasional small follicle was seen. The pulp was replaced by large numbers of cells corresponding to those in the rectal wall. The entire picture was that of a marked cellular hyperplasia in the pulp with replacement of many of the follicles. One curious feature was the apparently greater activity along the borders of the trabeculae, and in some instances there was an actual proliferation of cells in the trabeculae themselves.

Ovary: Surrounding the entire organ just beneath the peritoneal coat was a thin zone of cells of the type already described. Active growth was evinced by the fact that large numbers of mitotic figures were present. In the deeper-lying tissues, especially in the follicular remains (corpora albicantia), other foci of

hyperplasia were noted. In fact, all through the densest portion of the cortex occasional mitotic figures and monocytic cells were seen.

Uterus: Numerous collections of the typical cells were especially noticeable near the serous surface. These collections were almost invariably associated with small blood vessels. Unfortunately, the mucous surface was not included in the section submitted to us. Many of the small blood vessels in the muscular wall were filled with blood, and a high proportion of white cells were seen, which were mostly of the mononuclear type.

Summary of Histologic Picture: The mucosal and the submucosal reticulosis assumed the proportions of a tumor; there was a diffuse reticulosis of the spleen, of the ovary and of the uterus.

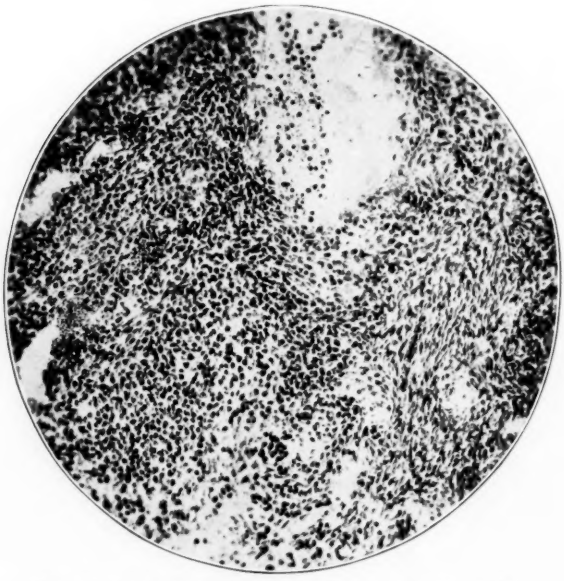

Fig. 7.—Photograph of tissue from the spleen; × 120.

SUMMARY AND CONCLUSIONS

1. The venous sinuses of the spleen and of the bone marrow and the lymph sinuses of the spleen and of the lymph glands probably are lined by differentiated reticular cells. These cells are similar to the Kupffer cells of the liver. Like the Kupffer cells, they are entirely different from the endothelial cells lining the ordinary blood and lymph channels.

2. The term "reticulo-endotheliosis" applied to monocytic leukemia does not elucidate the fact that the endothelial cells lining the ordinary blood and lymph vessels have nothing to do with the process. Neither does it attempt to distinguish between true reticulum and sinus reticulum (reticulo-endothelium).

3. Monocytic leukemia is probably a sinus reticulosis, whereas myeloid and lymphoid leukemia are probably true reticuloses.

4. There are good grounds for the conception that leukemia is a malignant neoplastic process. Malignant processes and neoplasia are closely associated in our minds with infiltration and with tumor formation. Specific focalization with tumor formation is apparently infrequent in leukemic sinus reticulosis (monocytic leukemia).

5. A case is recorded of acute monocytic leukemia in a young woman with localized mucosal and submucosal reticulosis in the rectal wall which assumed the proportions of a tumor. The tumor produced complete intestinal obstruction; clinically, the case exactly simulated carcinoma of the rectum with intestinal obstruction.

NOTE.—Since this article was prepared for publication another case of monocytic leukemia with formation of tumors has been observed at the Los Angeles County Hospital. The autopsy was performed by Dr. E. M. Butt, and tumors were noted in the pancreas, mesentery, heart, pleurae and diaphragm. The case will be reported later by Dr. Butt. Perhaps the occurrence of tumor formation in cases of monocytic leukemia is not as rare as has been supposed, and the lesion has possibly been interpreted as another type of neoplasm. The value of complete studies of the blood in all cases of tumors of obscure origin should be emphasized.

XANTHOMATOSIS GENERALISATA OSSIUM

REPORT OF A CASE SIMULATING OSTEITIS FIBROSA CYSTICA

DAVID H. SHELLING, M.D.
AND
ALLEN F. VOSHELL, M.D.
BALTIMORE

Since the introduction of parathyroidectomy as a cure for osteitis fibrosa cystica by Mandl,[1] in 1926, interest in generalized bone diseases has increased greatly. The numerous chemical and clinical observations on Recklinghausen's disease since 1926 have established certain criteria for arriving at the diagnosis of hyperparathyroidism and for use as a basis for exploring and possibly removing one or more hyperfunctioning parathyroids. The disease is usually first recognized clinically either through the history of a fracture or pain in an extremity or by the presence of calcic deposits in unusual sites, such as the skin or pelvis of the kidney; and the diagnosis is further corroborated by the discovery of cysts or areas of degeneration as shown in roentgenograms of the bones. The final diagnosis, however, depends on the results of the determination of the calcium and phosphorus concentrations in the blood and excreta. The typical chemical findings in osteitis fibrosa are: (1) hypercalcemia, (2) hypophosphatemia and (3) increased excretion of calcium in the urine, leading to (4) a negative calcium balance.

The typical cases of Recklinghausen's disease, presenting all the clinical and laboratory evidence indicative of hyperfunction of the parathyroids, offer little difficulty in diagnosis. However, cases of generalized disease of the bones, in which the cardinal clinical and laboratory signs are not clear, do present certain diagnostic problems. The difficulty may be due to several factors. Hypercalcemia, which is one of the most important diagnostic signs of hyperparathyroidism associated with osteitis fibrosa, has been encountered also in cases of multiple myeloma of the bones [2] and in cases showing osseous destruction as a result of infiltration or metastases by tumor cells.[3] Conversely, cases of Reck-

From the Harriet Lane Home of the Johns Hopkins Hospital and the Department of Pediatrics, Johns Hopkins University; and from the Kernan Hospital for Crippled Children and the Department of Orthopedics of the University of Maryland.

1. Mandl, F.: Arch. f. klin. Chir. **143**:1, 1926.
2. Barr, D. P., and Bulger, H. A.: Am. J. M. Sc. **179**:449, 1930.
3. Mason, R. L., and Warren, S.: Am. J. Path **7**:415, 1931.

Recklinghausen's disease may pass through periods in which hypercalcemia is not pronounced or is absent; an example is the case described by Wilder.[4] In this instance, high serum calcium levels were noted only after repeated chemical examinations of the blood. The roentgenograms also are not always helpful in the differential diagnosis, since the lesions of the bones supposedly typical of osteitis fibrosa may be simulated by other dystrophies of the osseous system. Similarly, the histologic structure of material obtained by biopsy from the bones and stained with the ordinary dyes may resemble that of osteitis fibrosa cystica, since fibrous replacement of osseous tissue is not pathognomonic of the histopathologic lesions of Recklinghausen's disease, as will be seen from the discussion of the case to be presented.

The necessity of arriving at a correct diagnosis becomes significant when surgical intervention is considered. If the osseous changes are due to hyperfunction of the parathyroids, parathyroidectomy is indicated; but if, on the other hand, the lesions in the bones are not associated with hyperparathyroidism, removal of parathyroid tissue is not to be considered.

We have recently encountered a case of dystrophy of the osseous system in a boy of 14 in which the roentgenograms and histologic studies of material removed by biopsy from one of the bones strongly suggested that the patient was suffering from Recklinghausen's disease, but the normal concentration of calcium and phosphorus in the serum and the apparently normal urinary excretion of calcium argued against it. A diagnosis of xanthomatosis generalisata ossium was finally made as the result of a second biopsy. Xanthomatosis was not definitely considered at first because the typical signs of xanthomatosis associated with the Schüller-Christian syndrome, namely, involvement of the calvarium, exophthalmos, diabetes insipidus and xanthomatosis cutis, were absent.

REPORT OF CASE

S. H., a white boy of 14, was transferred from the Kernan Hospital for Crippled Children to the Harriet Lane Home of the Johns Hopkins Hospital, Sept. 26, 1933, for study and observation.

His family and past histories were irrelevant. His present malady began two years previously, at which time he fell off a hay-loft, from a height of about 6 feet (2 meters). He felt pain in the left hip but was able to walk away. He was not aware of a fracture in the extremity, nor was he confined to bed immediately after the fall. Shortly after the accident, a limp appeared in the left leg and the patient tended to support his weight on the opposite leg. He consulted a physician, who referred him to the Emergency Hospital, Annapolis, for a roentgenographic examination. Because of the peculiar structure of the bone and the presence of a fracture in the neck of the left femur noted in the roentgenograms the patient was sent to one of us (A. F. V.) for orthopedic consultation, and admitted to the University Hospital for observation.

4. Wilder, R. M.: Endocrinology **13**:231, 1929.

The calcium concentration in the serum at that time was 10.9 mg. per hundred cubic centimeters, and the cytologic appearance of the blood, except for a moderate secondary anemia, was essentially normal. The urine was also normal. Roentgen examination of the long bones revealed cystlike areas as well as areas of sclerosis. The calvarium was not involved.

The patient was subsequently admitted to the Kernan Hospital for Crippled Children, where he remained from April 4, 1933, until July 23. Roentgenograms taken during that time showed the same changes previously noted, namely, a healed fracture in the neck of the left femur and areas of rarefaction, cystic formation and fibrosis in the humeri, radii and ulnas. The calcium and inorganic phosphorus concentrations of the serum were again within normal limits. A biopsy was performed on the left radius and the material was sent to the University Hospital for examination. The tissue removed from what appeared to be a cystic area was glistening white, and fibrous in appearance and consistency. The histologic sections, stained with hematoxylin and eosin, revealed a predominance of fibrous tissue, intermingled with spicules of bone and a few giant cells. The spicules of bone were surrounded by osteoid borders. Some of the sections contained, in addition, large, pale-staining, reticulated cells, resembling the foam cells seen in lipoid histiocytosis. But because of the infrequency of these cells and the predominance of the fibrosis, the significance of the foam cells was not fully appreciated at the time. On the basis of the roentgenographic and histologic observations and in spite of the negative results of the determinations of the calcium and phosphorus contents of the blood, a diagnosis of osteitis fibrosa cystica was strongly considered, but parathyroidectomy was deferred pending the outcome of more complete chemical studies of the blood and excreta.

The patient was sent home for the summer months and appeared to be doing well. However, on Sept. 18, 1933, he was readmitted to the Kernan Hospital because of loss of weight and increasing difficulty in using the left leg. The diagnosis of osteitis fibrosa cystica was still considered, but before parathyroidectomy was attempted, he was removed to the Harriet Lane Home of the Johns Hopkins Hospital for a study of the calcium and phosphorus metabolism.

On admission to the Harriet Lane Home, the patient's state of health was found to be essentially the same as that at the Kernan Hospital. He appeared rather small and underdeveloped for his age. The skin was clear. The lymph glands were not enlarged, and there was no visible or palpable enlargement in the neck in the region of the parathyroids. The head was of normal size and contour. The heart and lungs presented no abnormal physical signs. The liver and the spleen were not enlarged. The reflexes were normal and equal on the two sides. There was a marked limp of the left leg, and the patient carried most of his weight on the right leg. Irregular cortical thickenings were palpated in the long bones, especially in the upper third of the left humerus, the left greater trochanter, the phalanges of both hands and feet and the left fourth rib. The bony enlargements appeared hard and not painful to pressure. Crepitation was not noted. The left hip showed a prominent trochanter and coxa vara with consequent limitation of abduction and internal rotation. There was a marked scoliosis with a tendency to curvature to the left, and both a real and an apparent shortening of the left leg of 3.5 cm. was observed.

The calcium and phosphorus concentrations on September 27 were 9.6 and 4.6 mg. per hundred cubic centimeters, respectively, and on October 4, 9.8 and

3.8 mg. The concentration of plasma phosphatase was 8.4 units (Bodansky [5]), and the concentration of the blood cholesterol 221 mg. per hundred cubic centimeters. The cytologic appearance of the blood and the results of tests of renal function were normal; the Wassermann and tuberculin tests gave negative results.

Fig. 1.—Roentgenogram of the right humerus, radius and ulnas. Note the cystlike areas at the elbow joint and the tendency to fibrosis, especially in the humerus.

The roentgenographic report was as follows: "There was a multilocular cystic involvement of the left femur with apparent pathologic fracture of the neck; the left ileum and the left and right humeri, radii and ulnas showed similar processes.

5. Milligrams per hour per hundred cubic centimeters of plasma.

The destructive process had apparently expanded and thinned the cortex of these bones, although in some areas there was evidence of fibrous replacement and sclerosis."

After a few days on the ordinary hospital diet the patient was placed on a diet containing only 200 mg. of calcium daily. The urine was collected daily for a period of twelve days. The average daily excretion of calcium in the urine was 67.5 mg., the highest being 154.8 mg. and the lowest 44.4 mg. per day. The

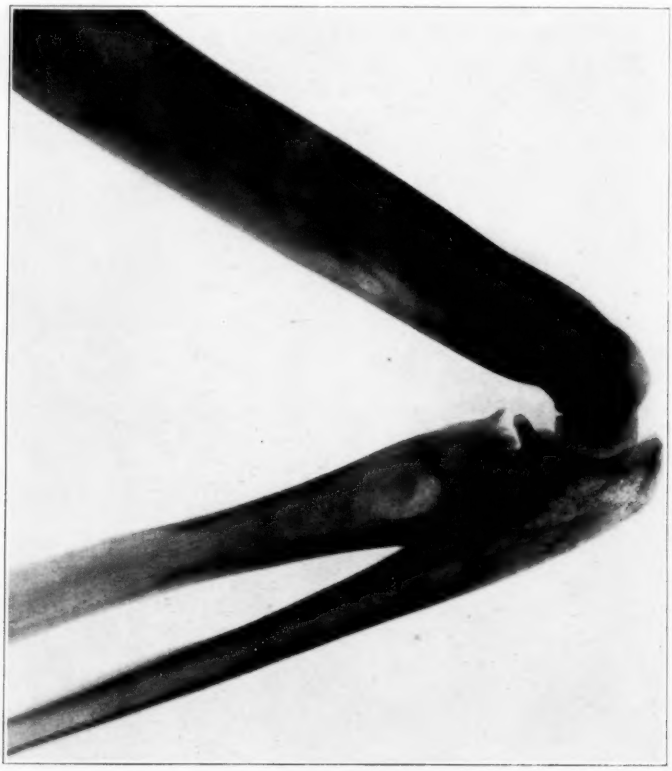

Fig. 2.—Roentgenogram of the left humerus, radius and ulna.

excretion of phosphorus averaged 314.3 mg. per day, the highest being 444 mg. and the lowest 250 mg. per day. Obviously, on this low calcium intake, the patient did not excrete excess amounts of calcium in the urine, as is usually the case in typical instances of Recklinghausen's disease.

During hospitalization and when at home, the patient showed no symptoms of polydipsia or polyuria. Xanthomatosis of the skin was also absent.

Reexamination at this time of the sections of the material obtained by biopsy led us to the conclusion that, in spite of the predominance of fibrosis and the presence of osteoid tissue, the numerous large, foamlike cells strongly suggested

that the lesions in the bones were in the nature of a lipoid granulomatosis. As the biopsy material had been dehydrated by being passed through alcohol and hence was defatted the presence of lipoid could not be determined by staining the remainder of the material with stains for fat. A second biopsy was, therefore, performed shortly after the patient returned to the Kernan Hospital. In contrast to the material obtained for the first biopsy, the tissue removed at the second

Fig. 3.—Roentgenogram of the left hip. Note the areas of rarefaction and the healed fracture in the neck of the femur.

operation was yellowish, granular and softer. Sections from this material were stained with sudan III as well as with eosin and hematoxylin. A description, by Dr. Paul G. Shipley, of the histologic appearance of this material follows:

In all sections, the spicules of bone appeared dense; obviously they must have been very hard. The endosteum was incomplete, and around most spicules of bone it was represented by a few scattered cells. The edges of the bony trabeculae

showed obvious signs of erosion, and in places one could see that the lacunae had been opened and the bone corpuscles left lying free. The lacunae were small, widely separated and few. Only occasional osteoclasts were present.

In the material examined at the first biopsy, some of the spicules of bone showed fairly wide osteoid borders as well as signs of former erosion. However, in the material studied at the second biopsy, osteoid tissue was absent. The meaning of this difference in the production of osteoid tissue is not clear. It is possible, however, either that different conditions prevailed in the different regions examined or that the osteoid tissue disappeared in the interval between biopsies, as a result of ultraviolet therapy.

The bony trabeculae in all the sections were widely separated by connective tissue, which in some areas was extremely dense. The fibers of the tissue were arranged in definite patterns between the spicules, often in broad, sweeping curves. The majority of these fibers seemed to be of the white variety. In certain areas, the fibers appeared to have undergone degeneration and to have become hyalinized. The cells of this tissue were numerous and consisted chiefly of connective tissue corpuscles. No traces of marrow were seen in the areas of fibrosis. Groups of cells, apparently osteoblasts, were present here and there.

The areas of fibrosis were fairly well vascularized by very small blood vessels, mostly capillaries. In some areas, the walls of the arterioles were unusually thickened, and in other places, the smaller arteries seemed to have participated also in this change. The nerves, when visible, had a normal appearance. Small hemorrhagic areas were seen in widely scattered areas of the connective tissue.

Parts of the intertrabecular tissue contained nests of huge cells with round or oval nuclei, usually eccentrically placed, and with a clear cytoplasm, which when stained with eosin and hematoxylin appeared to be a foamlike mass of tiny vacuoles (fig. 4). In sections stained with sudan III, these vacuoles were seen to be droplets of lipoid material. The nests of lipoid cells were scattered throughout the dense connective tissue in groups of varying sizes, sometimes even singly (fig. 5). These masses of foam cells undoubtedly represent xanthoma.

The grouping of these cells seemed to bear a definite relation to small blood vessels, which were wholly or partly surrounded by them. When a single xanthomatous cell existed alone, it was usually in apposition to a capillary.

On the basis of the histologic observations, and especially in the presence of an apparently normal amount of calcium and inorganic phosphorus in the serum and of a normal excretion of calcium in the urine, the diagnosis of xanthomatosis generalisata ossium seemed justifiable.

COMMENT

The case reported here illustrates the importance of considering lipoid granulomatosis as a possible cause of cystic degeneration and fibrosis of the long bones. Attention has recently been directed to this fact by Snapper and Parisel.[6] Their patient, a girl of 10 years, was operated on twice, but an adenoma of the parathyroid was not found. They were led to consider the possibility of xanthomatosis by obtaining, on one occasion, a cholesterol concentration in the blood of 322 mg. per hundred cubic centimeters and also by Kienböck and Meworach's[7] discussion of the difficulties in differentiating xanthomatous lesions of the

6. Snapper, I., and Parisel, C.: Quart. J. Med. **2**:407, 1933.
7. Kienböck, R., and Meworach, L.: Röntgenpraxis **4**:76, 1932.

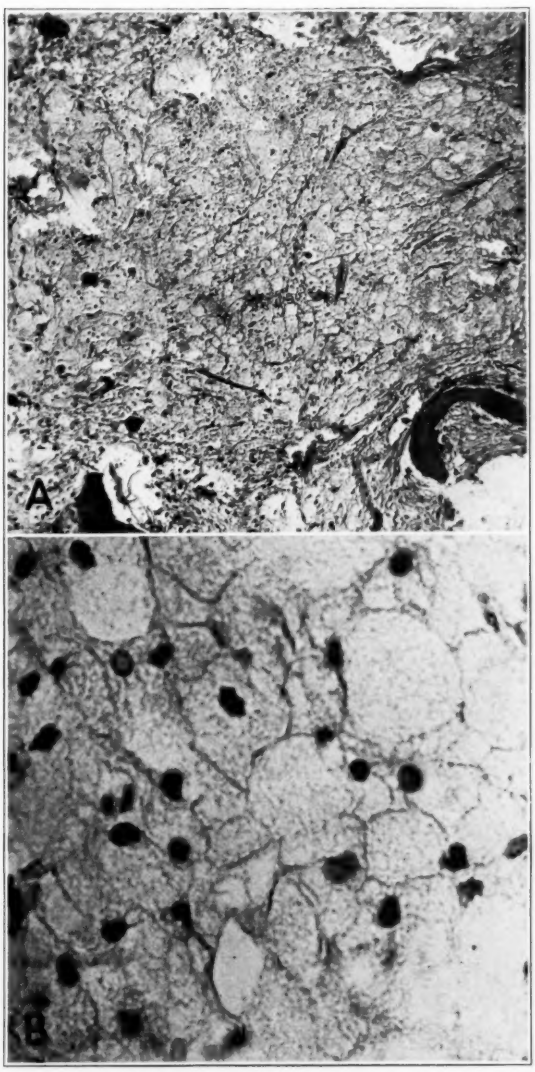

Fig. 4.—Sections of an area containing pale, large, reticulated foam cells: *A*, under low magnification, and *B*, under high magnification. Hematoxylin and eosin stain.

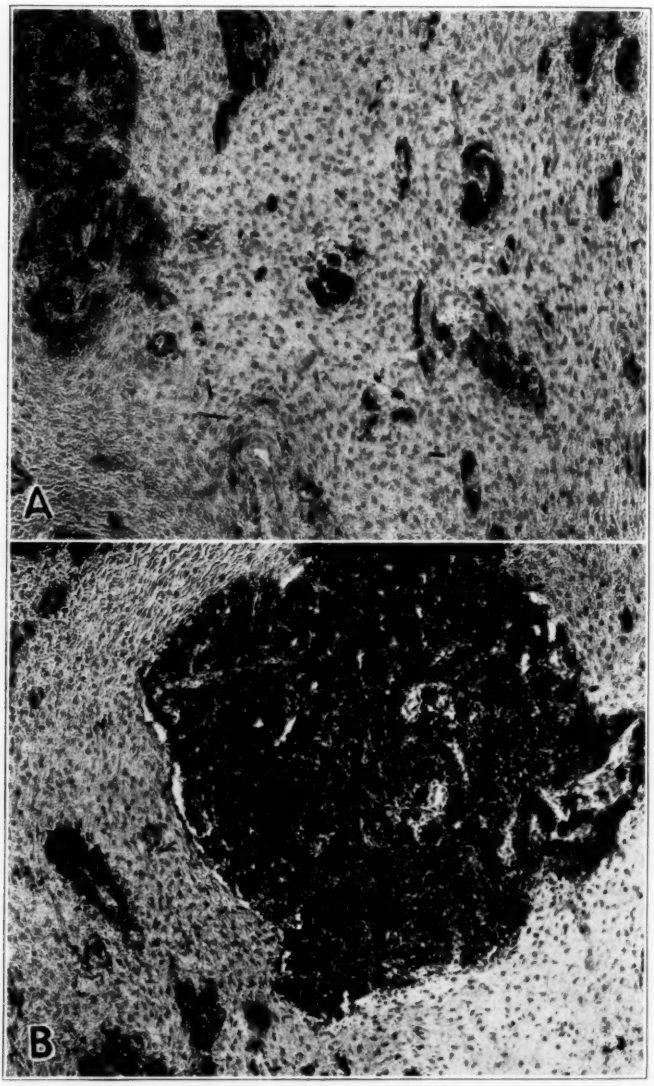

Fig. 5.—Islets of lipoid in an area of fibrosis: *A*, under low magnification, and *B*, under higher magnification (sudan III stain).

skeleton from true osteitis fibrosa cystica generalisata. The diagnosis was finally made, as in our patient, by a study of biopsy material removed for the second time from an affected bone. The histologic examination of this material showed "signs of osteitis fibrosa, but at the same time in the fibrous tissue great accumulations of foam cells loaded with double-refracting lipoids and fats."

Xanthomas are deposits of lipoids in large, swollen foam cells; they appear yellowish in gross section. Chester [8] termed such deposits of fats "lipoid granulomatosis," as against the common designation of "tumors," since xanthomas consist primarily of granulation tissue and not of tumor cells. The lipoid is composed, according to Epstein and Lorenz [9] and Kleinmann,[10] of large amounts of cholesterol and its esters, as contrasted with lecithin in Gaucher's disease and kerasin in Niemann-Pick's disease.

With the exception of xanthomatosis of the tendon sheaths, the most widely known clinical syndrome of xanthomatosis is Schüller-Christian's disease. Most of the cases belonging to this group possess the following clinical features: (1) multiple erosions of the bones of the skull; (2) exophthalmos, usually bilateral; (3) xanthomatosis cutis; (4) diabetes insipidus, and (5) retardation of growth, the majority of the patients being children. Xanthomatous infiltrations are also found, not infrequently, in the liver, spleen, lungs, kidneys and other organs of patients dying of the disease. The combination of xanthomatosis of the skull, skin and internal organs is not constant, and variations thus occur from the typical Schüller-Christian syndrome: (1) Xanthomatosis may be limited to the skin or internal organs without involving the bones; (2) it may be present in the long bones, as well as in the skull, skin and internal organs, or (3) it may be confined to the bones, or even to the long bones. In the past year, we have had occasion to observe three cases of xanthomatosis, including the present case, in which the symptoms were quite dissimilar. One presented xanthomatosis cutis and diabetes insipidus, without bone lesions; another showed the typical findings of Schüller-Christian's disease, including erosions of the long bones, whereas the case discussed here showed lesions of the long bones only, without involvement of the skin, internal organs or skull.[10a]

8. Chester, W.: Virchows Arch. f. path. Anat. **279**:561, 1930.

9. Epstein, E., and Lorenz, K.: Ztschr. f. physiol. Chem. **190**:44, 1930.

10. Kleinmann, H.: Virchows Arch. f. path. Anat. **282**:613, 1931.

10a. One of us (D. H. S.) recently saw another case of xanthomatosis ossium in which the lesions were limited to the calvarium, the left femur and the right clavicle. There were no other signs of Schüller-Christian's disease, and the concentrations of calcium and inorganic phosphorus of the serum were normal. Histologic sections, made from material removed for biopsy from a cystlike area in the clavicle, showed typical areas of xanthomatosis. The lesions healed under roentgen therapy.

Instances of other clinical and pathologic combinations have been collected by Henschen.[11]

Instances of xanthomatosis cutis and diabetes insipidus, without osseous erosions, are rather rare. They have been noted by Ausset,[12] Crocker,[13] Turner, Davidson and White,[14] Spillman and Wartin[15] and Pusey and Johnstone.[16] However, xanthomatous involvement of the long bones, in addition to that of the skull, skin and internal organs, is more common. Thus, in Hertzenberg's[17] case, xanthomatous tissue was present also in the femurs and vertebrae; in Hofer's[18] case, in the bone marrow; and in Moreau's[19] case, in the left ilium. Similar lesions of the long bones in addition to those of the cranium were also noted by Pende,[20] Barco,[21] Cignolini,[22] Alberti,[23] Schultz, Wermbter and Puhl,[24] Thompson, Keegan and Dunn,[25] Veit,[26] Rowland,[27] Sosman,[28] Ighenti,[29] Chester and Kugel,[30] Merritt and Paige[31] and Henschen.[11] In several of these cases, the roentgenograms of the long bones showed a great similarity to those of osteitis fibrosa, but the diagnosis of xanthomatosis was

11. Henschen, F.: Acta pædiat. (supp. 6) **12**:1, 1931.

12. Ausset, quoted by Henschen.[11]

13. Crocker, H. R.: Diseases of the Skin, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1903.

14. Turner, A. L.; Davidson, J., and White, A. C.: Edinburgh M. J. **32**:153, 1925.

15. Spillman, L., and Wartin, J.: Paris méd. **35**:193, 1920.

16. Pusey, W. A., and Johnstone, O. P.: J. Cutan. Dis. **26**:552, 1908.

17. Hertzenberg, H.: Virchows Arch. f. path. Anat. **269**:614, 1928.

18. Hofer, K.: Klin. Wchnschr. **9**:1302, 1930.

19. Moreau, J.: Arch. franco-belges de chir. **32**:697, 1931. Gohen, A.; Moreau, J., and Murdoch, J.: Rev. d'orthop. **17**:714, 1930.

20. Pende, N.: Riforma med. **45**:20, 1929.

21. Barco, P., cited by Snapper and Parisel.[6]

22. Cignolini, P.: Radiol. med. **16**:16, 1929.

23. Alberti, O.: Radiol. med. **11**:157, 1924.

24. Schultz, A.; Wermbter, F., and Puhl, H.: Virchows Arch. f. path. Anat. **252**:519, 1924.

25. Thompson, C. Q.; Keegan, J. J., and Dunn, A. D.: Defect of Membranous Bones, Exophthalmos and Diabetes Insipidus, Arch. Int. Med. **36**:650 (Nov.) 1925.

26. Veit, B.: Frankfurt. Ztschr. f. Path. **28**:1, 1922.

27. Rowland, R. S.: Xanthomatosis and the Reticulo-Endothelial System, Arch. Int. Med. **42**:611 (Nov.) 1928.

28. Sosman, M. C.: Am. J. Roentgenol. **23**:581, 1930; Xanthomatosis, J. A. M. A. **98**:110 (Jan. 9) 1932.

29. Ighenti, W. K.: Virchows Arch. f. path. Anat. **282**:585, 1931.

30. Chester, W., and Kugel, V. H.: Lipoidgranulomatosis (Type, Hand-Schüller-Christian), Arch. Path. **14**:595 (Nov.) 1932.

31. Merritt, K. K., and Paige, B. H.: Xanthomatosis (Schüller-Christian Syndrome), Am. J. Dis. Child. **46**:1368 (Dec.) 1933.

quite evident from the presence of other symptoms indicative of Schüller-Christian's syndrome.

The third variation of xanthomatosis, namely, involvement of the long bones without involvement of the skull or internal organs appears to be rare, but when present offers the greatest difficulty in differentiation from osteitis fibrosa cystica. A case of this type was reported by Kienböck and Meworach [7] in 1932, and another by Snapper and Parisel [6] in 1933. The case here reported is apparently the third instance in which the diagnosis of osteitis fibrosa cystica was first considered but the disease was subsequently demonstrated, histologically, to be xanthomatosis, or lipoid granulomatosis of the bones.

Kienböck and Meworach's patient showed spontaneous fracture and cystic degenerations in the upper third of the left femur, as well as some cystic areas in the dorsal vertebrae. On the basis of the appearance of the bones in the roentgenograms, Kienböck originally diagnosed the lesions as those of osteitis fibrosa cystica, although the expansion of the femur was not as marked as in advanced cases of Recklinghausen's disease. Five months afterward, a swelling was noted in the tenth rib, part of which was resected and examined histologically. The diagnosis, however, still remained obscure until the tissue was examined by Maresch, who finally established the diagnosis of lipoid granulomatosis.

Snapper and Parisel's patient, a mentally retarded girl, fell and fractured the femur at the age of 7 years. During the following two years she had five fractures of both femurs, one while turning over in bed. She was treated with preparations of calcium and ultraviolet irradiations, which apparently greatly benefited her. She had no more fractures and was able to walk, although deformities of both femurs and shortening of one leg were evident. The right humerus appeared swollen on palpation but was not painful. Roentgenograms of the long bones revealed osteoporotic lesions resembling multiple cysts, most pronounced in the right humerus. In this bone the degenerative process was extensive and caused the almost complete disappearance of the cortex at the affected sites. The calcium concentration of the serum was 12.6 mg. A diagnosis of osteitis fibrosa cystica was made and the patient was operated on twice, but no adenoma of the parathyroid was observed, in spite of the fact that the second exploration was extensive and was performed by a surgeon experienced in operations on the parathyroid. The diagnosis of xanthomatosis was suggested, as previously mentioned, by the observation of a blood cholesterol concentration of 322 mg. per hundred cubic centimeters, and by the resemblance of the roentgenograms of the bones to those in Kienböck and Meworach's case of xanthomatosis. The diagnosis was finally established by histologic examination of tissue removed, for the second time, from an area of

degeneration of the bone and the observation in this tissue of foam cells and lipoid-staining material.

Perhaps the case of Kienböck and Schenck [32] may be regarded as one of xanthomatosis ossium, although histologic proof is wanting. Their report concerned the case of a woman of 28 who had a fracture of the right humerus in 1927. Roentgenographic examination at that time revealed the fracture and, in addition, several central cysts. In 1928, cysts were also found in the left humerus. A diagnosis of osteitis fibrosa cystica was made, and in 1930 the patient was operated on, but an adenoma of the parathyroids was not found. In 1932, she had another fracture of the right humerus, and at this time the diagnosis of xanthomatosis was considered, but as a biopsy was not permitted, it was not confirmed histologically.

Chester [8] accidentally discovered a lipoid granuloma of the femur at autopsy on a man of 44. This led him to investigate for lipoid granulomatosis the bones of patients with xanthelasma of the eyelids. His search yielded but one positive result. He found a lipoid granuloma in the femur and another in the tibia of a man of 69. In neither of these cases were there signs of fracture or other clinical manifestations suggestive of involvement of the bones.

Localized xanthomatosis of a single bone has been described from time to time. Schroeder,[33] who reported the last case, mentioned four analogous cases described by Vermooten, Merrill, Kogius, and Zeyland and Dega. Schroeder's case also offered some difficulty in diagnosis. His patient had noted a swelling in the distal part of the fibula about seven years previously. A diagnosis of melanosarcoma was made after biopsy. Amputation was advised, but this was refused by the patient. Seven years later, a diagnosis of osteitis fibrosa was made and partly confirmed by histologic examination. The tumor was finally extirpated and was described by the pathologist as osteitis fibrosa with accumulations of cholesterol and foam cells.

Little is known of the etiology and pathogenesis of lipoid granulomatosis. In some cases, lipemia with hypercholesteremia has been noted, and hence the disease is considered to be due to a disturbance in lipoid metabolism. The lipemia, however, is not a constant characteristic, since the concentration of cholesterol in the blood seems to depend on the degree of activity of the granulomatous process. In the active stage, the cholesterol concentration in the blood may be high; during periods of quiescence, it may be within normal limits. In Snapper and Parisel's case, hypercholesteremia was noted only once; on other occasions, the cholesterol content of the blood was within the normal range. Tests

32. Kienböck, R., and Schenck, F.: Beitr. z. klin. Chir. **156**:237, 1932.
33. Schroeder, F.: Arch. f. klin. Chir. **168**:118, 1931.

for cholesterol tolerance performed by them also gave practically normal results. The cholesterol esters in the blood were, however, increased so that the greater portion of the lipoids of the blood consisted of cholesterol esters. Epstein and Lorenz [9] noted a similar disproportion between free cholesterol and cholesterol esters in the blood in cases of Schüller-Christian's disease, the concentration of the esters being nearly five times that of the free cholesterol. We have not determined the cholesterol esters in the blood of our patient, but the total cholesterol was only moderately elevated, 221 mg. per hundred cubic centimeters.

The mechanism of the infiltration of lipoids in the bones is also obscure. Chester [34] has expressed the belief that the basic lesion in lipoid granulomatosis is "a chronic, noninfectious, abacterial, inflammatory granuloma due to the deposition of various lipoid substances in the involved tissues," and that the inflammatory exudate is "a response of the tissues to the lipoid substances." He did not, however, venture an opinion as to the nature of the fibrosis ossium. The tendency of the lipoid to segregate about blood vessels, observed by Snapper and Parisel and by us, suggests the possibility that the fibrosis is present before the lipoid is conveyed for deposition in the proliferating connective tissue, but direct evidence for this suggestion is not available. We have attempted to produce infiltration of lipoids in the bones of rats by first inducing fibrosis by injections of parathyroid extract and then by feeding large amounts of cholesterol, but our efforts have been unsuccessful.

DIFFERENTIAL DIAGNOSIS

The difficulty in differentiating xanthomatosis ossium from osteitis fibrosa by roentgen, and even by histologic, examination demonstrates the necessity of complete studies of the metabolism of calcium and phosphorus and of staining the biopsy material for lipoids before parathyroidectomy is attempted. At this point it may be well to review the possible diagnostic points by which xanthomatosis may be differentiated from Recklinghausen's disease, although they are by no means infallible. They may be summarized as follows:

1. Pain. Absence of pain in the bones is infrequent in Recklinghausen's disease and common in xanthomatosis.

2. Swelling of the bones. In most cases of osteitis fibrosa cystica there are thinning of the cortex, expansion and swelling of the affected area and general osteoporosis. In xanthomatosis ossium, the swelling and expansion of the bone are usually slight or moderate, and the osteoporosis is localized.

34. Chester.[8] Chester and Kugel.[30]

3. Metastatic calcification. Calcic deposits in the soft tissues or the formation of renal calculi is more common in hyperparathyroidism than in xanthomatosis ossium.

4. Hypercalcemia and hypophosphatemia. Absence of hypercalcemia usually speaks against the diagnosis of Recklinghausen's disease, although, as previously mentioned, cases of hyperparathyroidism may, on rare occasions, pass through periods in which hypercalcemia is not pronounced or is absent. In hyperparathyroidism, hypophosphatemia is also fairly constant; in xanthomatosis ossium, the inorganic phosphorus of the serum is usually not reduced.

5. Phosphatase. In hyperparathyroidism the phosphatase of the plasma is increased to many times the normal value; in xanthomatosis, it is normal or but slightly increased. In our patient it was 8.4 units, the average normal for his age being 5 units.

6. Cholesteremia. Hypercholesteremia may be present in xanthomatosis. The increase may be more marked in the cholesterol esters than in the free cholesterol.

7. Hypercalcemia test in the rabbit. Hamilton and Schwartz[35] recently reported a test for the presence of a parathyroid hormone in the blood. This consists of determining the rise in the levels of serum calcium in a rabbit which has been given a definite amount of calcium chloride by stomach tube and which has received intramuscular injections of the blood to be tested. In hyperparathyroidism, the curve is much higher than normal; it may be compared to standard curves obtained by injecting graded amounts of parathyroid hormone and the same amount of calcium.

8. Calcium and phosphorus metabolism. In typical cases of osteitis fibrosa cystica, the constant abstraction of calcium from the bones produces a calciuria, so that when the patient is placed on a low calcium diet (100 to 200 mg. daily) the excretion of calcium in the urine usually exceeds many times the intake. In our patient, the results of such a test diet were entirely normal.

9. Biopsy. In Recklinghausen's disease, the introduction of a curet into a cystic area meets with no resistance, as if the instrument had passed into a cavity; while in xanthomatosis, the areas which appear cystlike in the roentgenograms may offer some resistance to the insertion of the curet, since these pseudocystic areas are composed of fibrous or sclerotic tissue rather than of necrotic or degenerated material.

10. Histologic appearance. The histologic appearance of the bones from patients with xanthomatosis ossium resembles closely that of osteitis fibrosa, and for this reason xanthomatosis may be easily mis-

35. Hamilton, B., and Schwartz, C.: Rickets and Hyperparathyroidism, Am. J. Dis. Child. **46**:775 (Oct.) 1933.

taken for the latter disease. Therefore, in every case showing dystrophy of the osseous system, especially without hypercalcemia, the biopsy material should be stained for lipoids, in order to establish or rule out the diagnosis of lipoid granulomatosis.

11. Course. In most cases of osteitis fibrosa, the condition does not improve spontaneously, whereas in the three cases reported by Kienbock and Meworach, Snapper and Parisel and ourselves, the disease process came to a standstill without resort to parathyroidectomy.

In addition to osteitis fibrosa cystica, xanthomatosis ossium may easily be confused with melanosarcoma, multiple myeloma, tuberculosis, syphilis, osteomyelitis and metastatic infiltrations of tumor cells. In melanosarcoma and in multiple myeloma, Bence-Jones' protein is noted in the urine, but this finding is by no means confined to these maladies. Bence-Jones' albuminuria may be present in other diseases not involving the skeletal system, or even in xanthomatosis, as occurred in Gilmore's patient.[36] Multiple tuberculous lesions of the bones are usually associated with tuberculous infections elsewhere in the body; the tuberculin test is positive, and there is a tendency to formation of sinuses. In syphilis, the Wassermann reaction is positive, other syphilitic manifestations may be present, and the lesions usually respond fairly promptly to antisyphilitic therapy. In acute osteomyelitis, there are fever and pain, and in the chronic form there is a tendency to sinus formation and the breakdown of tissues. Leukemia and Hodgkin's disease, involving the skeletal system, may occasionally simulate roentgenologically osteitis fibrosa or xanthomatosis. In these instances, a careful study of the blood cells and the presence of an enlarged spleen or of a generalized adenopathy usually reveals the true nature of the disease. Metastatic infiltrations from the thyroid, bronchi, stomach, breast, suprarenals or prostate should always be ruled out by careful physical examination. The age of the patient is of some diagnostic significance. Lipoid granulomatosis is more common in children and young adults, while neoplastic infiltrations are prevalent in older persons. A biopsy usually aids in ascertaining the correct diagnosis.

Xanthomatosis ossium must also be differentiated from other forms of lipoid granulomatosis, such as Gaucher's disease and Niemann-Pick's disease. In these diseases, the infiltrations are usually not limited to the bones, the liver and spleen being nearly always enlarged. Niemann-Pick's disease occurs in infancy and early childhood and is particularly frequent among Jews. The lipoid in Gaucher's disease is composed largely of lecithin, and in Niemann-Pick's disease, of kerasin, as against the predominance of cholesterol in xanthomatosis ossium or in Schüller-Christian's syndrome.

36. Gilmore, M. E.: Texas State J. Med. **21**:358, 1925.

No special therapy was instituted in the case of our patient. He received a balanced diet and frequent exposures to ultraviolet radiation. His general condition at present is stationary, and if the lesions do not improve spontaneously, high voltage roentgenotherapy will be tried on the basis of the beneficial results obtained locally with this form of therapy in Schüller-Christian's disease.[28]

SUMMARY

A case of generalized xanthomatosis, or lipoid granulomatosis of the bones, is described, in which the roentgenograms and histologic sections of biopsy material strongly suggested osteitis fibrosa cystica. The correct diagnosis was finally made by observing foam cells in some of the sections, by staining freshly removed material from the bone for lipoid and by finding a normal calcium balance.

The factors in the differential diagnosis of xanthomatosis ossium, osteitis fibrosa and other dystrophies of the skeletal system are enumerated and discussed.

HEART DISEASE IN PATIENTS WITH UTERINE MYOMA

A CLINICAL STUDY OF FIFTY CASES

FERDINAND FETTER, M.D.
AND
TRUMAN G. SCHNABEL, M.D.
PHILADELPHIA

The question as to whether or not uterine myoma causes heart disease has been argued since 1885 when Hofmeier [1] started the discussion by saying that he believed this type of tumor could injure the heart. Most of the early writers agreed with Hofmeier, although in 1890 Williams [2] expressed a contrary opinion when he said that in his experience, uterine fibroid was less often associated with heart disease than was any other pelvic lesion. Strassmann and Lehmann [3] in 1898 reported a series of 71 cases of uterine myoma in 34 per cent of which there was evidence of cardiac damage. These authors believed that the tumor could cause degenerative changes in the heart muscle. Other early writers who agreed with the views of Strassmann and Lehmann were Wilson,[4] Fleck,[5] Baldy,[6] Cumston,[7] Boldt [8] and Kessler.[9] The

From the Departments of Gynecology and Medicine, Philadelphia General Hospital.

Read before the section on General Medicine of the College of Physicians, Philadelphia, April 23, 1934.

1. Hofmeier, M.: Zur Lehre vom Shock (Ueber Erkrankungen der Circulationsorgane bei Unterleibsgeschwülsten), Ztschr. f. Geburtsh. u. Gynäk. **11**:366, 1885.

2. Williams, J. D.: The Co-Existence of Heart Disease and Pelvic Lesions, Edinburgh M. J. **36**:440 (Nov.) 1890.

3. Strassmann, P., and Lehmann, F.: Zur Pathologie der Myomerkrankung, Ztschr. f. Geburtsh. u. Gynäk. **38**:111, 1898

4. Wilson, Thomas: The Relation of Organic Affections of the Heart to Fibromyoma of the Uterus, Tr. Obst. Soc. London **42**:176 (May 2) 1900; The Cardiopathy of Uterine Fibromyoma, J. Obst. & Gynaec. Brit. Emp. **6**:107 (Aug.) 1904.

5. Fleck, Georg: Myom und Herzerkrankung in ihren genetischen Beziehungen, Arch. f. Gynäk. **71**:258, 1904.

6. Baldy, J. M.: The Mortality in Operations upon Fibroid Tumors of the Uterus, Am. J. Obst. **52**:370 (Sept.) 1905.

7. Cumston, C. G.: Cardiac Disease and Uterine Fibromyomata, New York M. J. **82**:893 (Oct. 28) 1905.

8. Boldt, H. J.: Uterine Myofibromata and Visceral Degeneration, New York M. J. **82**:887 (Oct. 28) 1905.

9. Kessler, L.: Myom-Herz-Ovarium, St. Petersburger med. Wchnschr. **22**: 421 (Oct. 8) 1905.

question as to whether secondary anemia from menorrhagia and metrorrhagia in these cases was not an important factor in producing cardiac symptoms was brought out early in the course of the discussion. However, Brasin [10] in 1893 discounted the importance of secondary anemia by pointing out that heart disease was less common in patients with carcinoma of the uterus and secondary anemia from hemorrhage than it was in patients with uterine myoma and secondary anemia.

Early authors who were not convinced that uterine myoma per se could cause heart disease were von Rosthon,[11] Winter [12] and Neu.[13] The latter was of the opinion that it was not logical to consider every cardiac disturbance occurring in a patient with a fibroid as being caused by a fibroid heart. He believed that the conception of the fibroid heart was not tenable, as proof of its existence was lacking. McGlynn [14] in 1914 reported the results of a study of 131 cadavers in which uterine myoma was found. He compared the cardiac findings at necropsy with the cardiac findings in a similar number of persons of the same age and sex in whom a tumor was not present. He reached the conclusion that the conception of a fibroid heart cannot be sustained, that uterine myoma is often associated with sclerotic lesions of the heart although it is not a cause of these lesions and that anemia resulting from hemorrhage from the tumor can affect the heart secondarily.

In the meantime other American authors were expressing their belief in the existence of an abnormal condition of the heart caused by myoma as a definite entity. Payne [15] in 1911 said that he believed that cardiac symptoms in patients with myoma are due not to secondary anemia but to the action of products of the uterine growth on the heart muscle. These views were concurred with by Doane [16] and by Barrows.[17] Several years later, beginning in 1921, various authors began to note a causal relationship between uterine myoma and arterial hypertension.

---

10. Brasin, cited by Kessler.[9]

11. von Rosthon, cited by Brickner, S.: Am. J. Obst. **62**:1027 (Dec.) 1910.

12. Winter, G.: Die wissenschaftliche Begründung der Indikationen sur Myomoperation, Ztschr. f. Geburtsh. u. Gynäk. **55**:49, 1905.

13. Neu, M.: Ueber die Beziehungen zwischen Herz und Myom, Ztschr. f. Geburtsh. u. Gynäk. **66**:688, 1910.

14. McGlynn, J. A.: The Heart in Fibroid Tumors of the Uterus, Surg., Gynec. & Obst. **18**:180 (Feb.) 1914.

15. Payne, R. L., Jr.: The Surgical Relationship Between Uterine Fibroids and Loss of Cardiac Compensation, J. A. M. A. **56**:1324 (May 6) 1911.

16. Doane, P. S.: Cardiac Changes Secondary to Uterine Myomata, Surg., Gynec. & Obst. **14**:42 (Jan.) 1912.

17. Barrows, C. C.: The Myoma Heart, Am. J. Surg. **26**:161 (May) 1912.

Vaquez and Leconte,[18] Heitz,[19] Müller[20] and later Vassitch[21] were among those who wrote on the subject. These views were partially confirmed by Alvarez and Zimmerman,[22] who found that the blood pressure of women with uterine myoma was higher than that of women of the same age without such a tumor, particularly among those in the fifth decade. However, they felt that the increased blood pressure and the uterine tumor were both a result of some underlying diathesis rather than that the tumor caused the increased blood pressure. Opposed to this view of a relationship between uterine myoma and hypertension was that expressed by Polak, Mittell and McGrath[23] who, in studying 416 patients with a uterine fibroid decided that there was no effect on the blood pressure attributable to the tumor in young women and that patients with uterine myoma who had high blood pressure were usually over 40 years of age, at which age the hypertension could be attributed to other causes.

The controversy continued. In 1924 Winter[24] again expressed his opinion that there was no evidence in favor of a cardiac lesion produced by uterine myoma alone and occurring only with uterine myoma. Strassmann[25] in 1925 decided that both uterine myoma and the cardiovascular damage that he found so often associated with it were caused by a dysfunction of the ovaries. This theory has not been confirmed. Brandman[26] in 1932 reported the case of a patient with severe secondary anemia due to uterine bleeding from a fibroid who was in a state of cardiac decompensation. Treatment of the anemia and removal of the tumor resulted in a return of compensation and a decrease in the size of the heart. Brandman stated that the only effect that a fibroid can have on the heart is a secondary one due to anemia.

---

18. Vaquez, H., and Leconte: Le passé, le présent et l'avenir des hypertendus, Paris méd. **2**:11 (July 2) 1921.

19. Heitz, J.: Hypertension et fibromes utérins, Bull. Acad. de méd., Paris **87**:422 (April 18) 1922.

20. Müller, F.: Die Bedeutung des Blutdruckes für den practischen Arzt, München. med. Wchnschr. **70**:1 (Jan. 5) 1923.

21. Vassitch, M.: Les fibromes utérins et l'hypertension artérielle, Gynéc. et obst. **24**:126 (Aug.) 1931.

22. Alvarez, W. C., and Zimmerman, A.: Blood Pressure in Women as Influenced by the Sexual Organs, Arch. Int. Med. **37**:597 (May) 1926.

23. Polak, J. O.; Mittell, E. A., and McGrath, A. B.: What Is the Relation of Hypertension to Fibroid Disease of the Uterus? Am. J. Obst. & Gynec. **4**:227 (Sept.) 1922.

24. Winter, G.: Myom und Herz, Ztschr. f. Geburtsh. u. Gynäk. **87**:225, 1924.

25. Strassmann, E.: Die Kreislaufänderung durch Klimakterium und Kastration, besonders bei Myom, Arch. f. Gynäk. **126**:169, 1925.

26. Brandman, H.: Fibromyoma of the Uterus, Cardiac Failure, Anemia and Edema, Arch. Int. Med. **50**:306 (Aug.) 1932.

The authors of textbooks on gynecology are still somewhat divided in their opinions on the question. Anspach [27] expressed the opinion that in patients with myoma around middle life arteriosclerosis is to be looked on as an associated lesion and not as a lesion produced by the myoma. Graves [28] in the 1928 edition of his "Gynecology" said that it is well to reserve judgment on the matter until the facts are better established. However, the same author writing in 1933 in Curtis' "Obstetrics and Gynecology" [29] decided that aside from functional changes that result from long-standing secondary anemia uterine myoma has no specific degenerative influence on the heart. The Crossens [30] were at least convinced that heart disease is present in a large percentage of patients with myoma. In the last edition of "Diseases of Women" it is stated that whether "the heart disturbances are due principally to chronic anemia from hemorrhage or to the direct action of some toxin produced in the myoma or constitute simply an associated product of the same condition that produced the myoma . . . whatever the cause . . . the fact remains that they are there and must be reckoned with." The Crossens summarized five series of cases of fibroid, there being a total of 951 patients; heart disease was present in 38 per cent of the total number, with a variation of from 25 to 47 per cent in the individual series. Fishberg [31] in his book on hypertension and nephritis expressed the same opinion as did the Crossens that cardiac manifestations in patients with uterine myoma are too frequent to be accidental. He did not look on the disturbances of the heart associated with myoma as a unitary concept, however, but said that the cardiac damage is due sometimes to anemia, sometimes to hyperthyroidism accompanying the myoma and sometimes to hypertension. Fishberg said: "The nature of the relation between fibroids and arterial hypertension, if any, is not clear."

In order to determine the incidence of cardiovascular damage in patients with uterine myoma and to decide whether or not there is such a clinical entity as the "myoma heart," 50 patients operated on consecutively for uterine myoma in the gynecological department of the Philadelphia General Hospital were studied thoroughly from a cardiovascular point of view. These patients were admitted to the hospital between October 1932 and August 1933. Only those patients operated

27. Anspach, Brooke M.: Gynecology, ed. 3, Philadelphia, J. B. Lippincott Company, 1927, p. 303.

28. Graves, William P.: Gynecology, ed. 4, Philadelphia, W. B. Saunders Company, 1928, p. 144.

29. Curtis, Arthur H.: Obstetrics and Gynecology, Philadelphia, W. B. Saunders Company, 1933, vol. 2, p. 779.

30. Crossen, H. S., and Crossen, R. J.: Diseases of Women, ed. 7, St. Louis, C. V. Mosby Company, 1930, p. 570.

31. Fishberg, Arthur M.: Hypertension and Nephritis, ed. 3, Philadelphia, Lea & Febiger, 1934, p. 520.

on were included in this series, so that there could be no question as to the correctness of the diagnosis. A few patients refused to permit surgical intervention, and for some it was not indicated. However, in none of the patients admitted and not operated on was cardiovascular disease a contraindication to operation.

METHOD OF STUDY

The patient's history was investigated minutely. Possible etiologic factors in the production of heart disease, such as syphilis, scarlet fever, diphtheria and rheumatic infections including sore throat, growing pains and chorea, were sought. Symptoms of cardiac disability, such as shortness of breath, swelling of the ankles, precordial pain and palpitation, were inquired about. A careful examination of the heart and peripheral arteries was made, including the effect of exercise on the blood pressure and the pulse rate. The eyegrounds were studied by an ophthalmologist. Other organs which might show the effect of cardiovascular disability, such as the lungs and the liver and the extremities, were included in the examination. The following special examinations were made: roentgenographic or fluoroscopic examination of the heart, either by means of a plate taken at 6 feet (182.8 cm.) or by an orthodiagram; electrocardiography; urinalysis; test for urea clearance; blood count; the Kahn or Wassermann test of the blood, and determination of the blood urea nitrogen. After the operation and before the patient left the hospital the heart was reexamined. If abnormalities were found in the preoperative electrocardiogram or orthodiagram, the examinations were repeated. From five to six months after the operation as many of the patients were reexamined as was possible, at which time electrocardiograms and orthodiagrams of those who had shown abnormalities were repeated. It was impossible to make the follow-up examination on 13 of the 50 patients, as they could not be found or would not come back to the hospital. Of the 13 patients not reexamined, 9 had normal cardiovascular systems, so only 4 patients with cardiac abnormalities were not studied in the follow-up.

OBSERVATIONS

Age and Race Distribution and Etiologic Factors.—The youngest patient was 26 years old; the oldest was 54. The distribution of the patients according to age and race is given in table 1. Table 2 shows the number of patients for whom the history of an etiologic factor or factors that could cause cardiovascular disability was found. Of the 2 patients with a history of rheumatism, 1 had had an attack of rheumatic fever, and the other gave a history of frequent sore throat and had typical rheumatic mitral valvulitis. Included among those having a history of syphilis are the patients who had a positive reaction of the blood to the Kahn or Wassermann test as well as those with a known history of antisyphilitic treatment. If the history was merely that of symptoms that might be due to syphilis, this was thought too indefinite to make a positive syphilitic history. In none of the patients who had had scarlet fever or diphtheria were these infections a cause of the existing heart disease. Both patients with a history of scarlet fever and 2 of the patients with a history of diphtheria had a normal heart.

Of the other 2 patients with a history of diphtheria, 1 had rheumatic heart disease and the other had hypertensive heart disease.

Symptoms Referable to the Cardiovascular System.—The evaluation of such symptoms as shortness of breath on exertion and swelling of the ankles as evidence of cardiac disability is difficult in the case of a patient with an abdominal tumor, as the tumor can easily produce such symptoms when no real cardiac damage is present. Shortness of breath was complained of by 13 patients (26 per cent). In 9 of the 13 the diagnosis of heart disease was subsequently made; in the other 4 no evidence of cardiovascular damage could be found in the physical or laboratory examinations. The dyspnea on exertion was therefore attributed to the presence of the tumor, which in all of these patients was

TABLE 1.—*Distribution According to Age and Race of the Entire Group*

	Number of Patients		
Age, Years	White	Negro	Total
20 to 29	0	7	7
30 to 39	0	27	27
40 to 49	3	11	14
50 to 59	1	1	2
Total	4	46	50

TABLE 2.—*Incidence of Possible Etiologic Factors Producing Heart Disease*

Etiologic Factors	Number of Cases	Percentage of Total Cases
Rheumatic infection (including all rheumatic manifestations)	2	4
Syphilis	18	36
Scarlet fever	2	4
Diphtheria	4	8

fairly large, averaging the size of a uterus which is three months pregnant. Three of these 4 patients were reexamined six months after the removal of the tumor, and in each case the dyspnea had practically disappeared. Swelling of the ankles toward evening was complained of by 7 patients (14 per cent). Six of these 7 were subsequently shown to have heart disease. In the other patient the edema of the ankles was attributed to the presence of the tumor. The subjective sensation of palpitation, usually in association with shortness of breath, was mentioned by 10 patients (20 per cent). All but 2 of these proved to have cardiac damage. No patient had precordial pain of the anginal type; only 1 patient had definite cardiac pain, and this was 1 of those who had a rheumatic lesion of a valve.

Cardiac Murmurs and Abnormal Sounds.—Accentuated Aortic Second Sound: Eight of the 50 patients had definite accentuation of the aortic second sound. Hypertension or aortitis or both were present, so that an explanation of this observation on the basis of pathologic change in the cardiovascular system was possible.

Systolic Murmur at the Apex: Thirteen of the 50 patients had this type of murmur. In 6 of them hypertension and cardiac hypertrophy were present, so it was believed that the murmur was evidence of relative mitral regurgitation. Two of the patients had a history of rheumatic infection, so the murmur was taken as evidence of rheumatic mitral valvulitis. In 1 of the 13 patients definite secondary anemia was present, so the murmur was considered to be hemic. For the 4 patients remaining, no explanation of the murmur other than that it was functional could be made. The presence of the murmur alone was not considered evidence of cardiac disease.

Systolic Murmur at the Aortic Area: Five patients had this type of murmur. In all of these hypertension or aortitis or both were present, so that, as in the case of the accentuated aortic second sound, an explanation of the murmur on a pathologic basis was possible.

Other Murmurs: One patient with a systolic murmur at the aortic area had a diastolic murmur, heard best at the aortic area and transmitted along the left border of the sternum. A diagnosis of aortic regurgitation as well as aortitis was made in this case. One of the rheumatic patients with an apical systolic murmur had also a presystolic murmur at this valve area; a diagnosis of mitral stenosis as well as mitral regurgitation was made in this case.

Blood Pressure.—A persistent systolic blood pressure reading of more than 140 mm. of mercury for patients under 40 years of age and of more than 150 mm. of mercury for patients over 40 years of age was considered abnormally high, and a persistent diastolic blood pressure reading of more than 90 mm. of mercury at any age was considered abnormal. These are the standards described by Gager [32] in his book on hypertension. On this basis, 34 of the 50 patients had normal blood pressure. The other 16 had hypertension.

Sclerosis of the Peripheral Arteries.—Thirty-five of the 50 patients had no palpable thickening of the radial arteries. The other 15 patients showed slight palpable sclerosis of these arteries, and 13 of the 15 had either hypertension or other signs of cardiovascular damage. The other 2 patients had no other signs of cardiovascular disease. This slight deviation from the normal in these patients, both of whom were over 40 years of age, was not thought sufficient to consider them as having cardiovascular disease.

Changes of the Eyegrounds.—Five of the 50 patients showed vascular changes in the fundus of the eye. One of these was a patient with chronic glomerulonephritis in whom retinal arteriolosclerosis without hemorrhages or exudates was found. The other 4 patients, who also showed arteriolosclerosis, were all in the hypertensive group.

32. Gager, Leslie T.: Hypertension, Baltimore, Williams & Wilkins Company, 1930, p. 49.

Roentgen Measurement of the Size of the Heart.—A cardiothoracic ratio greater than 1:2 was considered abnormal. On this basis 37 of the 50 patients showed no enlargement of the cardiac silhouette, and 12 of the remaining 13 showed enlargement of the transverse diameter of the heart or widening of the aorta, or both. The last of the 13 patients showed widening and tortuosity of the aorta without cardiac enlargement. In all the 13 patients hypertension, aortitis or a lesion of a valve was present to account for the abnormal silhouette.

Electrocardiographic Changes.—Electrocardiograms that showed left axis deviation or inversion of the T wave in lead III or both were not considered abnormal. The presence of occasional extrasystoles was also not considered abnormal.

Prominent Q Wave in Lead III Followed by an Inverted T_3: This electrocardiographic abnormality occurred in 2 patients before operation.

TABLE 3.—*Distribution According to Age and Race of the Patients with Hypertension*

Age, Years	Number of Patients		
	White	Negro	Total
20 to 29	0	0	0
30 to 39	0	5	5
40 to 49	2	7	9
50 to 59	1	1	2
Total	3	13	16

In both of these cases electrocardiograms taken after hysterectomy showed that the Q wave had disappeared. No other evidence of cardiovascular abnormality was found in these patients.

Changes in the T Waves in Leads I or II: Ten patients showed abnormalities of the T waves in lead I or II. The electrocardiograms of 3 patients showed either flattening or partial inversion of the T wave in lead I. In 2 of these, the change in the T wave persisted in the follow-up examination. One of these 2 patients was in the group with hypertension and the other had rheumatic mitral valvulitis. The patient in whom the change in the T wave did not persist showed no cardiac abnormality besides the electrocardiographic change. This will be discussed in detail farther on, along with the changes in the Q wave previously described.

Seven patients showed either flattening or inversion of the T wave in lead II, associated with inversion of T_3. In 2 of these the follow-up electrocardiogram showed a normal T wave in lead II. In 1 of these 2 patients no other cardiac abnormality had been found; the other was in the group with hypertension. For 1 of these 7 patients a follow-up electrocardiogram could not be obtained. No other cardiac abnormality had been shown in this case. Of the remaining 4 patients, 2 showed lessening of the abnormalities in the T wave in the follow-up exami-

TABLE 4.—*Significant Cardiac Findings in the Twenty-Five Patients with Evidence of Cardiovascular Abnormalities*

Group	Race	Age, Years	Electrocardiogram	Blood Pressure	Cardiac Enlargement	Valvular Lesions	Cardiac Diagnosis
I	Negro	29	T_1 and T_2 flat	150/85	Present	Mitral stenosis and regurgitation	Rheumatic mitral valvulitis
I	Negro	34	Right axis deviation; T_2 and T_3 inverted	130/88	Absent	Mitral regurgitation	Rheumatic mitral valvulitis
II	Negro	34	Normal	132/84	Absent	Aortitis	Syphilitic aortitis
II	Negro	32	Left axis deviation	140 to 158/ 50 to 70	Present	Aortic regurgitation	Syphilitic aortitis and aortic regurgitation
III	Negro	37	Normal	142 to 160/102 to 124	Absent	None	Chronic glomerulonephritis with hypertension
IV	Negro	37	Left axis deviation	160 to 180/ 90 to 110	Absent	None	Hypertensive heart disease
IV	Negro	42	Normal	160 to 190/ 90 to 120	Present	Relative mitral regurgitation	Hypertensive heart disease
IV	Negro	42	Normal	160 to 180/ 92 to 118	Present	None	Hypertensive heart disease
IV	White	48	Left axis deviation	160 to 180/ 94 to 110	Absent	Relative mitral regurgitation	Hypertensive heart disease
IV	Negro	39	Left axis deviation	140 to 180/ 95 to 120	Absent	None	Hypertensive heart disease
IV	Negro	48	Left axis deviation; T_2 and T_3 inverted	186 to 200/ 92 to 100	Present	Relative mitral regurgitation	Hypertensive heart disease
IV	Negro	48	Normal	162 to 174/104 to 118	Present	None	Hypertensive heart disease
IV	Negro	42	Normal	150 to 160/ 88 to 108	Present	None	Hypertensive heart disease
IV	White	42	Left axis deviation	140 to 172/ 96 to 100	Absent	Relative mitral regurgitation	Hypertensive heart disease
IV	Negro	43	T_2 and T_3 inverted	176 to 185/ 95 to 105	Absent	None	Hypertensive heart disease
IV	White	53	Left axis deviation	152 to 180/ 88 to 100	Present	None	Hypertensive heart disease
IV	Negro	42	Left axis deviation	180/120	Present	Relative mitral regurgitation	Hypertensive heart disease
V	Negro	54	Normal	160 to 180/100 to 110	Present	Aortitis	Hypertensive heart disease; syphilitic aortitis
V	Negro	32	Left axis deviation	150 to 180/112 to 130	Present	Aortitis	Hypertensive heart disease; syphilitic aortitis
V	Negro	31	Left axis deviation; T_2 and T_3 inverted	178 to 202/108 to 130	Present	Aortitis, relative mitral regurgitation	Hypertensive heart disease; syphilitic aortitis
VI	Negro	29	Left axis deviation; T_2 partly inverted; T_3 inverted; follow-up normal	110/ 65	Absent	None	Electrocardiographic changes only
VI	Negro	37	T_2 flat; T_3 inverted; follow-up, T_2 diphasic	122/ 78	Absent	None	Electrocardiographic changes only
VI	Negro	33	Left axis deviation; T_1 depressed; shading of all ventricular complexes; follow-up normal	108/ 70	Absent	None	Electrocardiographic changes only
VI	Negro	29	T_2 partly inverted; T_3 inverted; no follow-up	110/ 70	Absent	None	Electrocardiographic changes only
VI	Negro	27	T_2 and T_3 cove-shaped; follow-up: T_2 flat, T_3 inverted	108/ 78	Absent	None	Electrocardiographic changes only

nation, although the wave did not return to normal. Both of these patients showed no other cardiac abnormality besides the electrocardiographic changes, which will be discussed in detail later. In the case of the remaining 2 patients in this group the T wave remained inverted in the follow-up electrocardiogram. One of these had rheumatic heart disease, and the electrocardiogram showed, in addition to the changes in the T wave, right axis deviation, a P wave of increased amplitude and a top-normal P R interval. The other was a patient with hypertension.

Urea Clearance Test and Determination of Blood Urea Nitrogen.—A maximum urea clearance of from 80 to 125 per cent and a standard clearance of from 76 to 120 per cent were considered normal. On the basis of this test, 2 of the 50 patients showed a definite impairment of renal function. One showed 32 and 36 per cent standard clearance and the other, 25 and 27 per cent standard clearance for two one hour periods. In both of these patients the concentration of blood urea

TABLE 5.—*Incidence of the Various Types of Heart Disease*

Group	Type of Heart Disease	Number of Patients	Percentage of Cardiac Patients	Percentage of All Patients
I	Rheumatic	2	8	4
II	Syphilitic	2	8	4
III	Nephritic	1	4	2
IV	Hypertensive	12	48	24
V	Hypertensive; syphilitic	3	12	6
VI	Electrocardiographic changes only	5	20	10
	Total	25	100	50

nitrogen was slightly elevated (20 mg. and 25 mg. per hundred cubic centimeters, respectively). One had hypertension; the other did not, and neither had cardiac enlargement. A diagnosis of chronic glomerulonephritis was made in both cases.

Blood Count.—Only 1 of the patients had marked secondary anemia, i. e., a hemoglobin content below 60 per cent and a red blood cell count below 3,300,000. In this case the hemoglobin content was 50 per cent, and the red blood cell count was 2,820,000.

Size of the Tumor.—There was no relationship between the existence of heart disease and the size of the uterine myoma. The tumors varied in size from a mass 6 by 4 by 4 cm. to one the size of a uterus six months pregnant.

Deaths.—One patient died three months after the operation. She was a Negress 43 years of age with hypertensive heart disease and died of cerebral thrombosis. Autopsy was not performed.

Summary of All Cases.—Of the 50 patients exactly one-half showed no cardiovascular abnormality. Table 4 is a tabulation of the significant cardiac findings in the other 25 patients. These patients are divided into six groups, as shown in table 5.

COMMENT

Anemia and Heart Disease.—Secondary anemia due to hemorrhage from uterine myoma is considered an important factor in producing cardiac abnormalities in patients with myoma. However, in this series of 50 patients there was only 1 with anemia. She had an apical systolic murmur but no other evidence of cardiac damage. The murmur was therefore considered hemic, and she was thought to have a normal heart. Both the murmur and the anemia had disappeared six months after the operation.

Heart Disease Other than Hypertension.—The cardiac damage of the patients in groups I, II and III had obvious etiologic factors, that is, rheumatic infection, syphilis and chronic glomerulonephritis. The uterine myoma in these patients was obviously a coexisting lesion that had nothing to do with the production of heart disease.

Hypertension and Uterine Myoma.—The patients in groups IV and V, with hypertensive cardiovascular disease and uterine myoma, need a more detailed consideration. Those in group V had syphilitic aortitis as well as hypertension. That this combination is not uncommon was pointed out by Fishberg,[33] who showed also that there is no reason to believe that the syphilitic infection causes the hypertension.

If uterine myoma has any effect on the cardiovascular system (aside from that due to anemia), it either produces hypertension or is associated with an increased incidence of hypertension. The literature on this question has already been discussed. To decide whether this study indicates a relationship between uterine myoma and hypertension, it must be determined whether there is a greater incidence of hypertensive cardiovascular disease in our patients with uterine myoma than in other women of the same age and race.

Gager,[32] in a study of the incidence of essential hypertension in 1,000 women in the clinic of the Cornell Medical Center, New York, found the incidence by ten year periods to be as shown in table 6.

Patients with hypertension associated with aortic regurgitation or with glomerulonephritis were not included in this table. Gager's standards for increase in blood pressure have already been given. He did not state what proportion of the patients were Negro. An interesting and significant fact brought out by this study is that there is a sharp rise in the incidence of hypertension in women beginning at the age of 40, while in men this rise does not begin until a decade later. Risemann and Weiss [34] had previously made the same observation.

---

33. Fishberg,[31] p. 542.

34. Risemann, J. E. F., and Weiss, Soma: The Age and Sex Incidence of Arterial Hypertension, Am. Heart J. **5**:177 (Dec.) 1929.

Studies by various authors [35] on the relative incidence of hypertensive heart disease in Negroes and in white persons have shown that this type of heart disease is much more common in Negroes. In Stone and Vanzant's [35b] series, hypertensive heart disease was found twice as often in Negroes as in white persons, and in Schwab and Schulze's [35c] series the incidence was two and a half times greater. All of these investigators agreed that this type of heart disease begins earlier in Negroes and that its onset is especially early in Negro women.

We are safe in assuming that less than one third of the patients in Gager's series of patients were colored, as even in the southern clinics

TABLE 6.—*Gager's Figures on the Percentage of Incidence of Essential Hypertension*

Age, Years	Patients with Systolic Hypertension	Patients with Diastolic Hypertension
20 to 29	3.9	3.4
30 to 39	11.6	8.9
40 to 49	22.2	27.0
50 to 59	36.7	31.5

TABLE 7.—*Incidence of Hypertension in This Series Compared with That in Gager's Series* *

Age, Years	Total Number of Patients		Number with Hypertension		Percentage Incidence of Hypertension		Gager's Figures of Percentage Incidence of Systolic Hypertension
	White	Negro	White	Negro	White	Negro	
20 to 29	0	7	0	0	0	0	3.9
30 to 39	0	27	0	4	0	14.8	11.6
40 to 49	3	11	2	7	66.7	63.6	22.2
50 to 59	1	1	1	1	100.0	100.0	36.7

* The patient with nephritic hypertension is not included.

the ratio of white people to Negroes is about 2:1. The incidence of hypertensive heart disease in patients of this series in the 20 to 29 year group, in which no hypertension was found, is obviously less than in Gager's series. Its incidence in the 27 Negro patients in the 30 to 39 year group was lower than one might expect from Gager's figure for this decade, considering that this type of heart disease is at least twice as common in Negroes as in white people. In other words, the incidence of hypertensive heart disease in the patients with myoma under 40

35. (*a*) Wood, J. E.; Jones, T. D., and Kimbrough, R. D.: The Etiology of Heart Disease, Am. J. M. Sc. **172**:185 (Aug.) 1926. (*b*) Stone, C. T., and Vanzant, F. R.: Heart Disease as Seen in a Southern Clinic, J. A. M. A. **89**:1473 (Oct. 29) 1927. (*c*) Schwab, E. H., and Schulze, V. E.: The Incidence of Heart Disease and of the Etiological Types in a Southern Dispensary, Am. Heart J. **7**: 223 (Dec.) 1931. (*d*) Laws, C. L.: The Etiology of Heart Disease in Whites and Negroes in Tennessee, ibid. **8**:608 (June) 1933.

years of age is no greater, indeed probably less, than its general incidence in women of the same age and race.

For the patients over 40 years of age this statement is not true. The incidence of hypertensive Negro patients in the fifth decade in this series is higher than in Gager's series, even if one assumes that all of Gager's patients were white and that hypertension is two and a half times as frequent in the Negro as in the white race. The incidence of hypertension in the white patients in this series and in the patients over 50 years of either race is, of course, much higher than in Gager's series. The number of patients over 40 years of age (16) is, however, small as compared with the number of patients under 40 years (34), so that one must be careful in drawing conclusions about the older patients. It is significant that of the 12 patients with hypertension who were reexamined, from a total of 15, none showed a decrease in the blood pressure or a decrease in the size of the cardiac silhouette (if enlargement had been present before). In fact, in 3 of these patients the blood pressure was definitely higher at the follow-up examination than it had been before the operation. This increase may have been due to the production of an artificial menopause, but in any case it tends to disprove a causal relationship between the tumor and the hypertension.

The incidence of hypertension in the patients with myoma under 40 years of age is no higher than its general incidence in women of the same age and race. Thus there does not appear to be any connection between uterine myoma and hypertensive heart disease in women of this age. The increased incidence of hypertension in the patients in the fifth and sixth decades may indicate a possible connection in this age period. However, if there were any causal relationship between uterine myoma and hypertensive heart disease it ought to be evident before as well as after the age of 40. A larger number of women in the older age group must be studied before definite conclusions can be drawn.

Electrocardiographic Changes in Patients with Uterine Myoma.—It has already been said that the preoperative electrocardiograms of 2 of the patients showed a prominent Q wave in lead III followed by an inverted T wave. The postoperative electrocardiograms were normal, and no other evidence of cardiac disease was obtained. Figure 1 shows the preoperative and postoperative electrocardiograms for 1 of these patients. It was believed that the diaphragm made high by increased intra-abdominal pressure as a result of the tumor was responsible for these changes. Pardee [36] has reported, in the case of a pregnant woman, similar electrocardiographic changes which disappeared after delivery.

36. Pardee, Harold, E. D.: The Significance of an Electrocardiogram with a Large Q in Lead III, Arch. Int. Med. **46**:470 (Sept.) 1930.

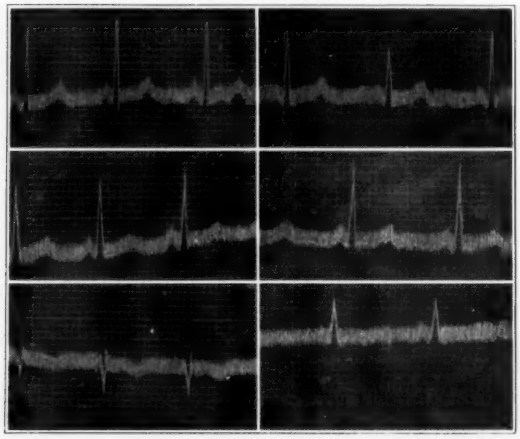

Fig. 1.—*A* is the preoperative electrocardiogram of patient 11 made on Nov. 2, 1932, showing a prominent Q wave in lead III followed by an inverted T_3 wave. The operation was performed on November 8. *B* is the electrocardiogram of the same patient made on Nov. 28, 1932, showing a return to normal.

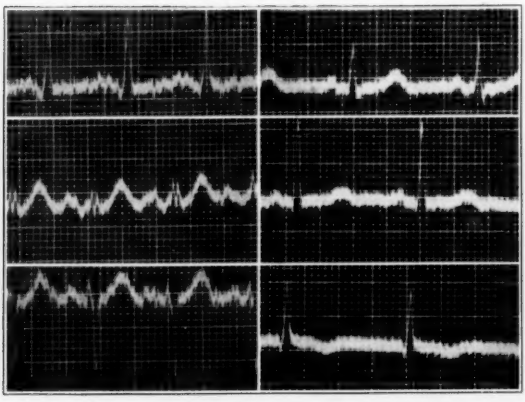

Fig. 2.—*A* is the preoperative electrocardiogram of patient 18 made on Jan. 14, 1933, showing the slurred Q R S complex in lead II and a depression of the T wave in lead I. The operation was performed on January 16. *B* is the electrocardiogram of the same patient made on June 15, showing a return to normal.

The electrocardiographic changes presented by the 5 patients of group VI (table 5) who showed no other evidence of cardiac damage are more difficult to explain. In the electrocardiograms of 2 of these patients the T wave had returned to normal in the follow-up examination. The electrocardiogram of 1 of these showed, before operation, partial inversion of the T wave in lead II associated with the inversion of T_3 and left axis deviation. After operation the left axis deviation and inverted T_3 remained, but the T wave in lead II was normal. This patient was of hypersthenic habitus with a horizontal type of heart, the width of which was top-normal. The electrocardiogram of the other of these 2 patients showed, before operation, left axis deviation, shading of the ventricular complexes in all leads, and

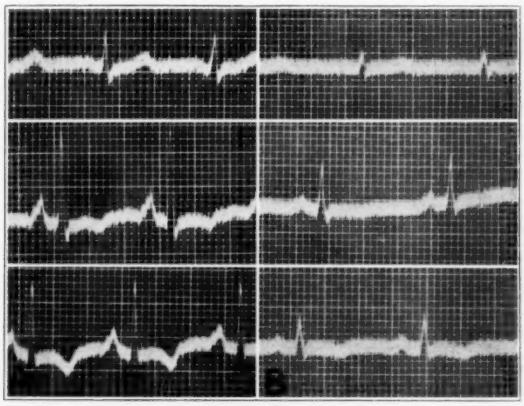

Fig. 3.—*A* is an electrocardiogram of patient 32, made on April 18, 1933, showing the cove-shaped T wave in leads II and III. The operation was performed on April 21, 1933. *B* is the electrocardiogram of the same patient, made on October 15, showing a flat T wave in lead II and an inverted T wave in lead III.

depression of the T wave in lead I. Six months after operation the electrocardiogram showed a normal condition. Figure 2 shows the preoperative and postoperative electrocardiogram of this patient. She was obese and the heart was of the horizontal type, although not as markedly so as was that of the record shown in figure 1.

Of the other 3 of the 5 patients, 1 showed before operation partial inversion of the T wave in lead II associated with inversion of T_3. A follow-up examination could not be obtained. She was obese, with a horizontal type of heart the width of which was top-normal. The remaining 2 patients showed changes in the T wave in lead II that were less marked in the follow-up examination than before the operation, but the wave had not returned to normal. Neither of the patients

was of hypersthenic habitus, and their hearts were not horizontal. The electrocardiogram of 1 of them before operation showed a flat T wave in lead II associated with the inversion of T_3. Subsequently T_2 became slightly diphasic while T_3 remained inverted. The preoperative electrocardiogram of the other patient showed the cove-shaped type of inversion of the T wave in leads II and III. Six months after the operation the T wave in lead II was flat, while that in lead III was inverted. Figure 3 shows the preoperative and postoperative electrocardiograms of this patient.

It is of course well known that the electrocardiogram is affected by the position of the patient in which the tracing is taken and by the position of the heart in the body. Cohn [37] has studied the effect of change of position of the heart on the electrocardiogram by changing the position of the electrodes on the wall of the chest. He was able to produce not only a change in the axis deviation but also an inversion of the T waves in all leads by this method. In order to produce an inversion of T_2, he had to rotate the electrodes enough to correspond to a change in the anatomic cardiac angle from a normal of $+46$ degrees to -74 degrees. To produce the inversion of T_1 and T_2 he had to rotate the electrodes enough to correspond with a cardiac anatomic angle of -114 degrees. In these patients with a fibroid the change in the position of the heart due to the tumor could not have been as much as this. Most of the fibroids were moderate-sized or large, although one was small (7 by 5 by 5 cm.), and this was in 1 of the patients in whose electrocardiogram the T wave was normal postoperatively. Thus the electrocardiographic changes do not seem to depend absolutely on the size of the tumor. None of the patients had complete inversion of T_1. The 2 patients whose T wave returned to normal after the operation had shown only partial inversion of the T wave, and both had the type of heart which goes with a high diaphragm. There is thus some evidence in favor of the view that the abnormalities of the T wave were due not to changes in the cardiac muscle but rather to a change in the position of the heart as a result of the abdominal tumor. The same applies, although not as clearly, to the 2 patients in whose electrocardiograms there was lessening of the abnormality of the T wave without complete return to normal. These 4 cases seem to indicate the possibility that abdominal tumors producing a change in the position of the heart result in alterations of the T wave in leads I and II of the electrocardiogram, although this study does not prove the point. In any case, we cannot consider these electrocardiographic changes occurring in patients with no other evidence of cardiac disease as conclusive evidence of cardiac damage.

37. Cohn, A. E.: An Investigation of the Relation of the Position of the Heart to the Electrocardiogram, Heart **9**:311 (Dec.) 1922.

SUMMARY AND CONCLUSIONS

In a series of 50 patients with uterine myoma 25 (50 per cent of the total) showed evidence of cardiovascular disease.

In 5 of these the only evidence of cardiac damage was in the electrocardiogram, consisting of changes in the T wave in leads I and II. The possibility that these electrocardiographic changes were due not to damage of the heart muscle but to change in the position of the heart as a result of the abdominal tumor is pointed out and discussed.

The percentage of patients with heart disease (40), not counting the 5 just mentioned, was found to agree closely with that of five series previously reported, totaling 951 patients with uterine myoma, which showed an average incidence of 38 per cent with a variation of from 25 to 47 per cent in the individual series.

There was no question of secondary anemia from uterine bleeding being a cause of heart disease in this series of patients. Only 1 of the 50 patients was anemic, and she proved to have a normal heart.

In 5 of the 20 patients with definite signs of cardiac disease, obvious etiologic factors other than the uterine myoma were present. In 2 of them the etiologic factor was rheumatic infection, in 2 it was syphilis and in 1 it was chronic glomerulonephritis.

The remaining 15 of the 20 patients had hypertensive heart disease. It is pointed out that it is this type of heart disease, if any, that may have uterine myoma as an etiologic factor.

The incidence of this type of heart disease in the patients of this series under 40 years of age was found to be no higher than its general incidence in women of the same age and race. This study therefore shows no relationship between uterine myoma and hypertension in the third and fourth decades.

The incidence of hypertensive heart disease in the patients in the fifth and sixth decades, however, was found to be higher than its general incidence in women of the same age and race. This might indicate a relationship between the two conditions at this age period. However, because there were relatively few patients in this age group, a larger number of older patients with myoma should be investigated before definite conclusions are drawn.

No indication was found in this study of any such clinical entity as the "myoma heart" in the sense of a type of heart disease caused by and occurring with uterine myoma alone.

1817 Pine Street.

1704 Pine Street.

JUVENILE DEMENTIA PARALYTICA

II. FAMILY HISTORY, WITH SPECIAL CONSIDERATION OF FAMILIAL NEUROSYPHILIS

WILLIAM C. MENNINGER, M.D.
TOPEKA, KAN.

This report, the second of a series of studies of juvenile dementia paralytica, is confined to an analysis of the family history, particularly the incidence of syphilis, neurosyphilis and mental disease. A previous report [1] covered the incidence, sex and age at onset. This study is based on 43 cases personally observed and 610 cases recorded in the literature.

INCIDENCE OF SYPHILIS IN FAMILY

Of the entire series of 653 cases the family history is detailed in 399 and is not given in 254. Syphilis in some form was demonstrated in one or more members of the family in 369 cases. Syphilis was demonstrated clinically or serologically (or both) in the mother in 223 cases, in the father in 226 cases and in one or more of the siblings in 114 cases.

Syphilis in the Mother.—It is a recognized, established fact that the mother of a syphilitic child is herself syphilitic. Consequently one may correctly assume that maternal syphilis is present in every case of juvenile dementia paralytica. It is of interest, however, to summarize the incidence of maternal syphilis in this series as shown either by clinical or by serologic evidence (or by both). In the 399 cases of juvenile dementia paralytica (in which the family history is recorded), in 223 instances the mother was demonstrated to have syphilis. The types of maternal syphilis are shown in table 1.

Thus syphilis was demonstrated in the mother in 56 per cent of the 399 cases of juvenile dementia paralytica in which the family history is reported. It is certain that in many cases the family, including the mother, was not available for study, and in many reports no mention is made of any investigation as to the family history. Nevertheless, in 34.1 per cent of the entire series of 653 cases of juvenile dementia paralytica, the mother presented either clinical or serologic evidence (or both) of syphilis.

An analysis of table 1 shows three points: 1. Of the 223 instances in which maternal syphilis was demonstrable the patient was male in 59 per cent and female in only 39 per cent.

From the Menninger Clinic.

1. Menninger, W. C.: Juvenile Paretic Neurosyphilis Studies: I. Incidence, Sex, and Age at Onset, Am. J. Syph. & Neurol. **18**:486 (Oct.) 1934.

2. The mother had neurosyphilis in 58 cases, representing 26 per cent of all the demonstrable cases of maternal syphilis; this figure does not include possible cases of asymptomatic neurosyphilis, since investigation of the spinal fluid was not carried out as a routine. In most instances such an investigation would have been impossible even though considered desirable by the investigator. The inclusion of the asymptomatic cases would increase the percentage of cases of neurosyphilis considerably. But the incidence of neurosyphilis of 26 per cent in the group of 223 mothers is much higher than the incidence in average groups of female patients with syphilis. The incidence of clinical neurosyphilis in syphilis in females was given by Moore [2] as 6.4 per cent, a figure which represents one-fourth the frequency found in the mothers of the patients with juvenile dementia paralytica. It appears that the mothers of neurosyphilitic offspring show a much higher incidence of neurosyphilis than an average group of female syphilitic patients.

TABLE 1.—*Incidence of Syphilis in the Mother*

Type of Syphilis in Mother	Total Number of Cases	Cases in Boys	Cases in Girls	Cases in Which Sex Was Not Stated
Syphilis without neurosyphilis	165	100	65	0
Dementia paralytica	30	20	10	0
Other forms of neurosyphilis	28	12	13	3
Total	223	132	88	3

3. The table shows approximately an equal distribution of dementia paralytica and other forms of neurosyphilis in the mothers; from this fact one may conclude that there is no female predisposition in the transmission of dementia paralytica.

A more detailed analysis of the 165 cases of maternal syphilis (not including neurosyphilis) is given in table 2 which shows the association of the maternal syphilis with other instances of syphilis or mental disease in the family.

The data presented in table 2 do not permit any significant conclusions; they merely call attention to the frequency of association of demonstrable syphilis in the mother with syphilis and mental disease in other members of the family. In approximately 50 per cent of the cases, some other member of the family besides the mother was demonstrated to have syphilis or mental disease.

Syphilis in the Father.—In 399 cases of the total series of 653 cases of juvenile dementia paralytica information is given regarding the family history. In these 399 cases the father presented clinical or serologic

2. Moore, J. E.: Studies in Asymptomatic Neurosyphilis: III. The Apparent Influence of Pregnancy on the Incidence of Neurosyphilis in Women, Arch. Int. Med. **30**:548 (Nov.) 1922.

evidence (or both) of syphilis in 226 instances; the syphilitic involvement is classified as to type in table 3.

Thus paternal syphilis was demonstrated in 56.7 per cent of the 399 cases of juvenile dementia paralytica in which sufficient family history was recorded. In the entire series of 653 cases, paternal syphilis was demonstrated in 34.6 per cent.

TABLE 2.—*Incidence of Late Stages of Syphilis (Excepting Neurosyphilis) in the Mother* *

Associations with Syphilis or Mental Disease in the Family			Cases in Boys	Cases in Girls	Total Number of Cases
Maternal and paternal syphilis			29	27	56
With mental disease in nonsyphilitic member of family	2♂	0♀			
With congenital syphilis in one or more offspring	3♂	5♀			
With paternal neurosyphilis	3♂	10♀			
With congenital syphilis in offspring and mental disease in nonsyphilitic member in family	1♂	0♀			
With no data except presence of syphilis in parents	20♂	12♀			
	29♂	27♀			
Maternal syphilis (paternal syphilis absent or unknown)			71	38	109
Syphilis in one or more offspring	13♂	9♀			
Juvenile dementia paralytica 4♂ 1♀					
Syphilis without neurosyphilis 9♂ 8♀					
	13♂	9♀			
With mental disease in nonsyphilitic member of family	3♂	1♀			
With syphilis in mother only	55♂	28♀			
	71♂	38♀			
Total maternal syphilis (excluding maternal neurosyphilis)			100	65	165

* In this and in subsequent tables the following terms are used: "maternal" and "paternal" refer to the mother and father of the patient with juvenile dementia paralytica. "Family" includes brothers or sisters and uncles and aunts of the patient. "Offspring" refers to other children with congenital syphilis, brothers or sisters of the patient. "Mental disease" includes hypophrenia, neurotic and psychotic illnesses and instances so designated occurring in nonsyphilitic members of the family so far as is known. "Siblings" refers to brothers or sisters of the patients with juvenile dementia paralytica.

TABLE 3.—*Incidence of Syphilis in the Father*

Type of Syphilis in the Father	Total Number of Cases	Cases in Boys	Cases in Girls	Cases in Which Sex Was Not Stated
Syphilis without neurosyphilis	146	97	49	0
Dementia paralytica	57	34	23	0
Other forms of neurosyphilis	23	15	2	6
Total	226	146	74	6

An analysis of table 3 reveals further information. In the 226 instances of paternal syphilis the patient was male in 64.6 and female in only 32.7 per cent of the cases. In the entire series of cases surveyed in this study the males represented 57 per cent and the females 43 per cent; these figures, when compared with the percentage of patients

of each sex having a demonstrable paternal syphilitic history, suggest a predisposition of paternal transmission to males. Furthermore, table 3 indicates an incidence of 35.4 per cent of neurosyphilis (in the 226 cases) in the fathers, a figure which again is higher than the average incidence of neurosyphilis in males. The incidence of clinical neurosyphilis in male syphilitic patients was given by Moore [2] as 20.38 per cent, a figure representing nearly half of the incidence of clinical neurosyphilis in the fathers of our patients with dementia paralytica. The figures also show more than twice as frequent occurrence of dementia paralytica as of all other types of neurosyphilis in

TABLE 4.—*Occurrence of Late Syphilis (Excluding Neurosyphilis) in the Father*

Associations with Syphilis or Mental Disease in the Family			Cases in Boys	Cases in Girls	Total Number of Cases
Paternal and maternal syphilis			30	19	49
With mental disease in nonsyphilitic member of family	2♂	0♀			
With congenital syphilis in one or more offspring	3♂	5♀			
With maternal neurosyphilis	4♂	2♀			
With congenitally syphilitic offspring and mental disease in nonsyphilitic member of family	1♂	0♀			
With no data except presence of syphilis in parents	20♂	12♀			
	30♂	19♀			
Paternal syphilis (maternal syphilis absent or unknown)			67	30	97
With congenital syphilis in one or more offspring	8♂	6♀			
With congenital neurosyphilis in one offspring	0♂	3♀			
With mental disease in nonsyphilitic member of family	2♂	1♀			
With syphilis in father only	57♂	20♀			
	67♂	30♀			
Total paternal syphilis (excluding paternal neurosyphilis)			97	49	146

the fathers. This fact suggests a paternal predisposition to transmit dementia paralytica.

A more detailed analysis of the 146 instances of paternal syphilis (excluding neurosyphilis), showing the association of syphilis and mental disease in other members of the family, is shown in table 4.

Table 4 again indicates the predominance of the condition in male offspring over that in female children, the ratio being approximately 2 to 1, and these figures are also suggestive of a tendency to predisposition in males. Besides this point there are no obvious conclusions.

Syphilis in Both Parents.—It was demonstrated either clinically or serologically (or both) that both parents had some form of syphilis in 72 cases. In 19 instances one parent had neurosyphilis; in 6 instances both had dementia paralytica; in 4 instances both had some form of neurosyphilis other than dementia paralytica, and in 43 instances both had syphilis without involvement of the central nervous system. The

distribution and further analysis of these cases is presented in table 5. An analysis of this table shows that of 72 cases of juvenile dementia paralytica in which both parents were syphilitic, in 29 (40.3 per cent) at least one parent and in 10 cases (14 per cent) both parents had neurosyphilis. In 9 of these 10 cases, the offspring were male. It is of interest to note that in the 13 cases in which the father had dementia paralytica and the mother had another type of syphilis (not neurosyphilis), the offspring with dementia paralytica was female in 10 instances. Furthermore, 4 of the offspring were male in the 6 instances in which the mother had dementia paralytica and the father had syphilis without involvement of the central nervous system.

TABLE 5.—*Syphilis in Both Parents*

Type of Syphilis and Association with Syphilis and Mental Disease in Other Members of Family			Cases in Boys	Cases in Girls	Total Number of Cases
Syphilis, other than neurosyphilis			26	17	43
With one or more congenitally syphilitic offspring	3♂	5♀			
With congenitally syphilitic offspring and mental disease in nonsyphilitic member of family	1♂	0♀			
With mental disease in nonsyphilitic member of family	2♂	0♀			
No data except syphilis in both parents	20♂	12♀			
	26♂	17♀			
Neurosyphilis in one or both parents			16	13	29
Neurosyphilis other than dementia paralytica in both parents	3♂	1♀			
Dementia paralytica in both parents	6♂	0♀			
Paternal dementia paralytica, maternal syphilis, not neurosyphilis	3♂	10♀			
Maternal dementia paralytica, paternal syphilis, not neurosyphilis	4♂	2♀			
	16♂	13♀			
Total number of patients with both parents with syphilis			42	30	72

Syphilis in the Siblings.—In the entire series of 653 cases of juvenile dementia paralytica some data were given about the family history in 399 instances. Many of the records, however, did not mention the presence or absence of syphilis in the siblings, even though they contained information regarding the mother and father. This is probably due in part to difficulty in securing contact with other members of the family which was experienced in many of the cases personally observed. In a small percentage of cases the patient was an only child.

Consequently the data on the incidence of syphilis in the brothers and sisters of the patient are probably inadequate. Syphilis was demonstrated in the brothers and sisters of 49 male and of 38 female patients with juvenile dementia paralytica, a total of 87 instances.

A detailed analysis of these 87 cases showing the relationship to different types of parental syphilis and also the occurrence of mental

disease in a nonsyphilitic member of the family is given in table 6. It should be pointed out in the interpretation of this table that the incidence of maternal syphilis includes only the cases with clinical or serologic evidence (or both) of syphilis. Thus in 54 cases of juvenile dementia paralytica with congenital syphilis in brothers and sisters the mother was not reported as being syphilitic, though it is an established

TABLE 6.—*Incidence of Congenital Syphilis in the Brothers and Sisters*

Associations with Syphilis and Mental Disease in the Family			Cases in Boys	Cases in Girls	Total Number of Cases
Congenital syphilis in brothers and/or sisters and syphilis in both parents			5	7	12
No data except syphilis (not neurosyphilis) in both parents	3♂	5♀			
Dementia paralytica in mother; syphilis, not neurosyphilis, in father	1♂	0♀			
Dementia paralytica in father; syphilis, not neurosyphilis, in mother	0♂	2♀			
No data except both parents with dementia paralytica	1♂	0♀			
	5♂	7♀			
Congenital syphilis in brothers and/or sisters and maternal syphilis (paternal syphilis absent or unknown)			10	11	21
Mental disease in nonsyphilitic member of family	0♂	1♀			
Maternal syphilis, not neurosyphilis	9♂	8♀			
Maternal dementia paralytica	1♂	2♀			
	10♂	11♀			
Congenital syphilis in brothers and/or sisters and paternal syphilis; maternal syphilis absent or unknown			10	7	17
Paternal syphilis, not neurosyphilis	8♂	6♀			
Paternal dementia paralytica	2♂	1♀			
	10♂	7♀			
Congenital syphilis in brothers and/or sisters; paternal syphilis absent or unknown			24	13	37
No data except congenital syphilis in brothers and/or sisters	22♂	12♀			
Mental disease in nonsyphilitic member of family	2♂	1♀			
	24♂	13♀			
Total number of cases with congenital syphilis in brothers and/or sisters			49	38	87

fact that the mother of every congenitally syphilitic child is herself syphilitic. It must be assumed in these 54 cases that the mother either was not examined or did not present clinical or serologic evidence of syphilis at the time of the examination.

Because the error resulting from the failure to report the status of siblings is great it seems inadvisable to draw any definite conclusions from the figures in table 6.

INCIDENCE OF NEUROSYPHILIS IN THE FAMILY

Of special interest in this study is the incidence of neurosyphilis in other members of the family.

Of the 399 cases (of the total series of 653 cases) in which definite information about the family history was obtained, in 143 cases (36.8 per cent) neurosyphilis was present in one or more members of the family. Even if one assumes that there was no neurosyphilis in the family in any of the 254 cases in which no family history was given (which is very improbable) the 143 cases represent 22.5 per cent of the total of 653 cases, a remarkably high incidence of neurosyphilis. This figure is even more significant when one considers that this series does not include cases of asymptomatic neurosyphilis; the patients all showed clinical as well as serologic evidence of neurosyphilis. The percentage of clinical neurosyphilis is about 10 per cent as contrasted to this figure of 22.5 per cent. The figure for dementia paralytica represents less than 5 per cent of the incidence of all the manifestations of late

TABLE 7.—*Incidence of Neurosyphilis in the Family*

Type of Neurosyphilis and Member of Family Involved				Cases in Boys	Cases in Girls	Cases in Which Sex Was Not Stated	Total Number of Cases
Dementia paralytica				49	47	..	96
In both parents	6♂	0♀					
In mother	14♂	10♀					
In father	23♂	28♀					
In siblings	5♂	9♀					
In uncle	1♂	0♀					
	49♂	47♀					
Neurosyphilis other than dementia paralytica				24	14	9	47
In both parents	3♂	1♀					
In father	12♂	1♀	6				
In mother	9♂	12♀	3				
	24♂	14♀	9				
Total number of cases with neurosyphilis in family				73	61	9	143

syphilis (Turner [3]), in contrast to 14.7 per cent as observed in this series of parents and brothers and sisters of patients with juvenile dementia paralytica. Tables 8 and 9 indicate the incidence of maternal, paternal and fraternal dementia paralytica and their associations with syphilis and mental disease in the family.

The obvious fact shown in tables 8 and 9 is that juvenile dementia paralytica is not transmitted consistently to a member of the same sex as was suggested by Frölich.[4] In this series 20 sons with juvenile dementia paralytica and only 10 daughters with the disease were born to a total of 30 mothers with dementia paralytica. In the 57 instances of paternal dementia paralytica the offspring were female in 23 and male in 34 cases. The unusual association of dementia paralytica in both

3. Turner, T. B.: The Race and Sex Distribution of the Lesions of Syphilis in Ten Thousand Cases, Bull. Johns Hopkins Hosp. **46**:159, 1930.

4. Frölich, W.: Ueber allgemeine progressive Paralyse der Irren vor Abschluss der körperlichen Entwicklung, Inaug. Dissert., Leipzig, Bruno Georgi, 1901.

the father and the mother is recorded in 6 instances (Major,[5] McDowall,[6] Baudouin and Lévy-Valenski,[7] Sträussler,[8] Lafora[9] and Menninger[10]). My own case has not previously been reported in detail.

CASE 7.[11]—A white youth, aged 19, was admitted to the institution in which his father and mother had died of dementia paralytica. There were no other siblings. Though the patient was retarded in learning to walk, until the age of 8 or 9 years he had been regarded as unusually bright and intelligent. At the age of 8 he fell from a merry-go-round, striking the back of his head. At 10 he

TABLE 8.—*Incidence of Dementia Paralytica in the Mother*

Association with Syphilis and Mental Disease in Family	Cases in Boys	Cases in Girls	Total Number of Cases
Dementia paralytica in father	5	0	5
Dementia paralytica in father and congenital syphilis in sibling	1	0	1
Syphilis, not neurosyphilis, in father	4	2	6
Congenital syphilis in siblings	0	2	2
Congenital syphilis in siblings and mental disease in family	1	0	1
Mental disease in nonsyphilitic member of family	2	0	2
No data except dementia paralytica in mother	7	6	13
Total	20	10	30

TABLE 9.—*Incidence of Dementia Paralytica in the Father*

Association with Syphilis and Mental Disease in Family	Cases in Boys	Cases in Girls	Total Number of Cases
Dementia paralytica in mother	5	0	5
Dementia paralytica in mother and congenital syphilis in sibling	1	0	1
Syphilis, not neurosyphilis, in mother	4	8	12
Syphilis, not neurosyphilis, in mother and congenital syphilis in sibling	0	2	2
Congenital syphilis in sibling	2	1	3
Mental disease in nonsyphilitic member of family	4	1	5
Dementia paralytica in relative other than mother of sibling	2	0	2
No data except dementia paralytica in father	16	11	27
Total	34	23	57

5. Major: General Paralysis in a Boy, Brit. M. J. **2**:1339, 1892.

6. McDowall, C. F. F.: General Paralysis in Father, Mother and Son, J. Ment. Sc. **54**:562, 1908.

7. Baudouin, A., and Lévy-Valenski, J.: Paralysie générale juvénile chez une malade dont le père et la mère sont morts de paralysie générale, Encéphale **2**:490, 1910.

8. Sträussler, E.: Ueber Entwicklungsstörungen im Zentralnervensystem bei der juvenilen progressiven Paralyse und die Beziehungen dieser Erkrankung zu den hereditären Erkrankungen des Zentralnervensystems, Ztschr. f. d. ges. Neurol. u. Psychiat. **2**:30, 1910.

9. Lafora, G. R.: Zur Histopathologie der juvenilen Paralyse mit Mitteilung zweier Fälle, Ztschr. f. d. ges. Neurol. u. Psychiat. **15**:281, 1913.

10. Menninger, W. C.: Juvenile Dementia Paralytica: Study of Forty Cases, J. A. M. A. **95**:1499 (Nov. 15) 1930.

11. Cases 1 to 6 have been reported in Menninger, W. C.: Juvenile Dementia Paralytica. I. Incidence, Sex and Age at Onset, Am. J. Syph. & Neurol. **18**: 486 (Oct.) 1934.

began to ramble in his speech, talking in a silly manner, and talipes began to develop. The latter condition grew worse, but the patient did not become incapable of locomotion until the age of 14. His vision became impaired at about 13, and since he was 17 the family had doubted whether he could see. For five years he had been unable to speak intelligibly, and dysphagia had been marked. He was completely helpless on admission. Physically he was markedly emaciated; he showed contractures of the lower limbs and athetoid movements of the fingers. The neurologic findings included fixed, unequal, irregular pupils, a bilateral Babinski sign, exaggerated, bilaterally equal deep reflexes and ankle clonus on the left. No stigmas were present. Laboratory data were not available.

The patient could take only a liquid diet and vomited occasionally. Rhythmic jerky movements of the head developed. He died three months after admission; the duration of the disease was approximately ten years.

There are references to some other cases in which the mother and father had dementia paralytica, though none can be verified. One author, Amelien, has been rather widely cited as reporting 6 such cases, but no references are given. A French worker, Ameline,[12] in 1900 did report

TABLE 10.—*Incidence of Dementia Paralytica in Brothers and Sisters*

	Total Number of Males	Total Number of Females	Total Number of Cases
Dementia paralytica			
In other brothers or sisters alone	0	8	8
With syphilis, not neurosyphilis, in father	0	3	3
With syphilis, not neurosyphilis, in mother	4	1	5
With mental disease in the family	1	0	1
Total number of cases in which brothers or sisters had dementia paralytica	5	12	17

6 instances in which dementia paralytica occurred in a parent and an offspring; in 4 instances in the father and son; in 2, in the mother and daughter, and in 1, in a maternal uncle and a nephew. However, none of his cases were presumed to be definite instances of congenital syphilis, and he did not give sufficient evidence to decide the point.

The incidence of dementia paralytica in the brothers or sisters is indicated in table 10.

There are, according to this table, 17 instances in which some other sibling in the family had juvenile dementia paralytica. There are reports of 2 cases in which three members of the same family were affected: that of Homén,[13] who cited the case of three girls, aged 12, 20 and 21 and that of Kingery,[14] whose patients were aged 2, 4 and 7 years. Cases similar to those of Kingery recently came under my observation.

12. Ameline: De l'hérédité et en particulier de l'hérédité similaire dans la paralysie générale, Ann. méd.-psychol. **11**:459, 1900.

13. Homén, E. A.: Eine eigenthümliche Familienkrankheit, unter der Form einer progressiven Dementia, mit besonderem anatomischen Befund, Neurol. Centralbl. **9**:514, 1890.

14. Kingery, L. B.: A Study of the Spinal Fluid in Fifty-Two Cases of Congenital Syphilis, J. A. M. A. **76**:12 (Jan. 1) 1921.

Three boys, aged 7, 5 and 3, had parents who showed no clinical evidence of syphilis and had negative Wassermann tests of the blood, though both had received antisyphilitic treatment. The paternal grandmother had been treated for syphilis. The boy aged 7¼ years was sickly as a baby, ate poorly and was said to have rickets. He never walked alone and acquired a vocabulary of about fifty words. In his third year he began sitting around doing nothing, and it was noted that his pupils were unequal. He was treated for "thyroid trouble." Convulsions began in the fourth year, and in the fifth the spinal fluid was found to have a positive Wassermann reaction. On examination he showed marked hydrocephalus, pes cavus, advanced chorioditis, bilateral optic atrophy, fixed unequal pupils, apparent deafness, a bilateral Babinski sign and Hutchinson's teeth. The Wassermann reaction of the blood was positive, but the spinal fluid could not be examined. The second child, a boy aged 5¼ years, appeared to be in good health till 4 months of age when "stomach trouble" developed. He walked at 13 months, talked at 15 months and seemed to develop normally. At the age of 5 years he became sulky, refused to obey and was irritable, abusive and much less talkative than formerly. He presented unequal, nearly fixed pupils, used a pronounced baby talk and showed an inability to respond to the simplest commands, hyperactive deep reflexes and a positive Wassermann reaction of the blood. The third child, a boy aged 3⅓ years, sat up at 6 months and walked at 17 months, but his legs seemed weak and he resorted chiefly to crawling. He developed physically and seemed well until 3 years of age, when an infection of the scrotum developed from a splinter. Following this, an ankle and then one knee became swollen. He presented pupils nearly fixed to light, hyperactive deep reflexes and a tremendous hydrocephalus.

Other reports of two children with juvenile dementia paralytica in the same family were given by Hoch,[15] Jouschenko (1896), von Speyr (1899, the mother was tabetic), Sollier (1910), Trapet (1910), Huguet (1913), Kron (1915), Müller-Hess (1919, the mother had tabes), Grütter (1920), Long-Landry (1921, the father was tabetic and two other children had neurosyphilis), Klauder and Solomon,[16] Potter [15] and myself.[10]

Familial Predisposition to Neurosyphilis in Three Generations.—While the occurrence of syphilis in the third generation seems fairly well established,[17] it is extremely rare and difficult to prove beyond question. There are, however, several reported cases in which neurosyphilis appeared in three successive generations; this may certainly indicate a familial predisposition to neurosyphilis, even when the direct transmission is doubtful. In the aforementioned family of three boys with congenital neurosyphilis, the paternal grandmother had syphilis beyond doubt, and from the description given it was likely neurosyphilis, though

15. To avoid duplication, a bibliography listing all individual reports of cases will be given at the conclusion of a subsequent study.

16. Klauder, J. V., and Solomon, H. C.: Juvenile Paresis, with Presentation of Twenty-Three Cases, Am. J. M. Sc. **166**:545 (Oct.) 1923.

17. Sams, W. M.: Third Generation Syphilis, Am. J. Syph. & Neurol. **17**:492. 1933.

no examination was possible. The following case also indicates the presence of probable neurosyphilis in three generations:

CASE 8.—A girl was aged 14 on admission. At least three grandparents were treated for syphilis, and one grandfather died at 54 of tabes. The father, mother and one brother all attended the clinic for syphilitic patients at the Bellevue Hospital and had positive Wassermann tests of the blood. Another brother, aged 16, was mentally defective. The patient had a normal birth and developed normally until vision began to fail at 9 years and was completely gone at 10 years. She had always been a bright child, of happy disposition; she had many friends, liked to study and was quiet and obedient. She was fond of music and played the piano well for her age. At 13 years of age she became nervous, and twitchings of the right arm developed. She became irritable and sleepless and stopped attending school at 14 because of nervousness. She became resistive and at times excited and stubborn. Ten days before admission she became disturbed, laughed and cried alternately, rolled on the floor and tore off her clothes. Physically she was well developed and well nourished. Neurologically she showed optic atrophy, fixed pupils, coarse nystagmus, defects of speech, incontinence and an absence of the knee jerk on the left. She had an ataxic gait. Stigmas were not present. Mentally she was alternately mute and noisy, restless and depressed. She was resistive, negativistic and gave no cooperation, and restraint was occasionally necessary. Laboratory examination showed positive Wassermann tests of the blood and spinal fluid, increased globulin, no cells and a colloidal gold curve of 4554332110.

She had received two months' treatment with arsphenamine before admission. She was given tryparsamide regularly for the following eleven months; malaria therapy was regarded as inadvisable because of her general condition. She showed slight improvement, but she remained silly and no change occurred in the physical signs. Her parents thought that she was better and paroled her eleven months after admission.

In 1910, Lwoff and Condomine [18] reported a case of juvenile dementia paralytica in a girl, aged 20, whose maternal grandmother and mother had dementia paralytica; two aunts and an uncle suffered from mental disease; a cousin was feebleminded, and four other siblings were mentally deficient; one of these committed suicide. Leavitt [19] reported a case of juvenile dementia paralytica in a boy whose maternal grandmother had tabes; the mother had syphilitic disease of the optic nerve and a positive Wassermann test of the spinal fluid. Klauder and Solomon [16] quoted Rieger (reference not given or located) as reporting a family in which the father, son, daughter and granddaughter all had dementia paralytica.

Neurotropic Strain of Spirochaeta Pallida.—The fact that in 36.8 per cent of the cases in which the family history is known there was evidence of neurosyphilis in some other member of the family is strong

18. Lwoff and Condomine, A.: Un cas de paralysie générale juvénile, Informateur d. alien. et d. neurol. **5**:39, 1910.

19. Leavitt, F. H.: Juvenile Dementia Paralytica Occurring in the Third Generation of a Syphilitic Family, Arch. Neurol. & Psychiat. **26**:665 (Sept.) 1931.

clinical evidence toward the theory of the existence of a neurotropic strain of S. pallida. However, it is only clinical evidence and not conclusive proof of the existence of such a strain.

Clinical evidence of the existence of syphilis *à virus nerveux* has been extensive, too much so to be reviewed here. Marie [20] reviewed the subject of a neurotropic strain in cases of hereditary syphilis of the nervous system and gave a hundred references. The studies of Junius and Arndt,[21] von Rohden,[22] Plaut and Goering,[23] Semper,[24] Wahl [25] and Bonneau [26] on the occurrence of neurosyphilis in the descendants of parents with dementia paralytica have been strongly suggestive of the existence of such a strain of spirochetes. And the studies on conjugal neurosyphilis of Junius and Arndt,[21] Schacherl,[27] Raven,[28] Seelert [29] and Moore and Kemp [30] have also supported such a hypothesis. Kemp and Poole's [31] study of the incidence of neurosyphilis among the parents of congenitally syphilitic children is especially suggestive: In a group of 20 families with congenitally neurosyphilitic children and in a group of 20 families with congenitally syphilitic children without neurosyphilis, they found that neurosyphilis was eight times as frequent among the mothers and over three times as frequent among the fathers in the neurosyphilitic group. They pointed out, however, that familial predisposition to neurosyphilis may be just as much a factor as a possible neurotropic strain.

---

20. Marie, A.: Hérédo-syphilis et paralysie générale infantile, Bull. Soc. franç. de dermat. et syph. **33**:153 (March) 1926.

21. Junius, P., and Arndt, M.: Ueber die Deszendenz der Paralytiker, Ztschr. f. d. ges. Neurol. u. Psychiat. **17**:303, 1913.

22. von Rohden, F.: Ueber die Pathologie der Paralytikerfamilie, Ztschr. f. d. ges. Neurol. u. Psychiat. **37**:110, 1917.

23. Plaut, F., and Goering, M. H.: Untersuchungen an Kindern und Ehegatten von Paralytikern, München. med. Wchnschr. **58**:1959, 1911.

24. Semper: Les enfants des paralytiques généraux, Thèse de Paris, 1904.

25. Wahl: Contribution à l'étude de la descendance des paralytiques généraux, Thèse de Paris, 1898.

26. Bonneau: L'hérédité similaire dans la paralysie générale, Thèse de Paris, 1909.

27. Schacherl, M.: Ueber Luetikerfamilien, Jahrb. f. Psychiat. u. Neurol. **36**: 521, 1914.

28. Raven, W.: Serologische und klinische Untersuchungen bei Syphilitiker-Familien, Deutsche Ztschr. f. Nervenh. **51**:342, 1914.

29. Seelert, H.: Untersuchungen der Familienangehörigen von Paralytikern und Tabikern auf Syphilis, Monatschr. f. Psychiat. u. Neurol. **41**:329, 1917.

30. Moore, J. E., and Kemp, J. E.: Studies in Familial Neurosyphilis: III. Conjugal Neurosyphilis, Arch. Int. Med. **32**:464 (Sept.) 1923.

31. Kemp, J. E., and Poole, A. K.: Familial Neurosyphilis: IV. Incidence of Neurosyphilis Among the Parents of Congenitally Neurosyphilitic Children, J. A. M. A. **84**:1395 (May 9) 1925.

There is, however, clinical evidence against such a theory. There are numerous recorded instances of neurosyphilis affecting several members of a family, each acquiring syphilis from a different source (Moore and Keidel [32]), as Stewart [33] pointed out. Furthermore, it is rather common to find patients with juvenile dementia paralytica without stigmas or cutaneous or osseous syphilis whose brothers or sisters show pronounced stigmas or cutaneous or osseous syphilis. Dennie [34] expressed the belief that there is only slight clinical evidence of transmission of dementia paralytica from parents to their offspring; the malady may develop in the first child, and the others may escape without any clinical form of neurosyphilis.

Moore [35] has summarized the experimental evidence by stating that the problem is not proved. He reviewed the unconfirmed work of Reasoner [36] with a strain of spirochetes particularly prone to produce chorioretinitis in rabbits. Levaditi and Marie's [37] work on differentiation of neurotropic and dermotropic strains has been especially questioned by Jahnel,[38] who believed that they confused their neurotropic strain with Treponema cuniculi, the organism of spontaneous spirochetosis in rabbits. The unconfirmed work of Plaut and Mulzer [39] with a strain which causes a high proportion of rabbits to show pleocytosis in the spinal fluid was uncontrolled with regard to the confusing factor of spontaneous encephalitis in rabbits.

Consequently, the hypothesis of the existence of a neurotropic strain must still be left in the balance, despite clinical evidence. Certainly the clinical evidence mustered could be equally applied to the theory of a familial predisposition to neurosyphilis. And furthermore it is likely

---

32. Moore, J. E., and Keidel, A.: Studies in Familial Neurosyphilis: II. Familial Neurosyphilis from Various Extra-Marital Sources: A Clinical Contribution to the Question of Neurotropism, J. A. M. A. **80**:1818 (March 24) 1923.

33. Stewart, R. M.: Juvenile Types of General Paralysis, J. Ment. Sc. **79**:602 (Oct.) 1933.

34. Dennie, C. C.: Familial Neurosyphilis, J. A. M. A. **95**:1571 (Nov. 22) 1930.

35. Moore, J. E.: The Modern Treatment of Syphilis, Springfield, Ill., Charles C. Thomas, Publisher, 1933, p. 36.

36. Reasoner, M. A.: Some Phases of Experimental Syphilis with Special Reference to the Question of Strains, J. A. M. A. **67**:1799 (Dec. 16) 1916.

37. Levaditi, C., and Marie, A.: Etudes sur le tréponème de la paralysie générale, Ann. Inst. Pasteur **33**:741, 1919.

38. Jahnel, F.: Das Problem der progressiven Paralyse, Ztschr. f. d. ges. Neurol. u. Psychiat. **76**:166, 1922.

39. Plaut, F., and Mulzer, P.: Die Liquordiagnostik im Dienste der experimentellen Kaninchensyphilis, München. med. Wchnschr. **69**:496, 1922.

that there are determining factors, as yet undefined and possibly unsuspected, inherent in the subject which may be far more important than the strain or virulence of the infecting organisms.

INCIDENCE OF MENTAL DISEASE IN THE FAMILY

Exclusive of dementia paralytica, mental disease sufficiently severe to necessitate hospitalization occurred in 55 instances in the 399 cases in which the history is known. This figure represents not the entire number of mentally ill relatives but rather the number of cases of

TABLE 11.—*Incidence of Mental Disease in the Family*

Association with Syphilis			Cases in Boys	Cases in Girls	Total Number of Cases
Both parents syphilitic			4	0	4
Both parents with syphilis, not neurosyphilis	2♂	0♀			
Congenital syphilis in siblings	1♂	0♀			
Paternal dementia paralytica and maternal syphilis, not neurosyphilis	1♂	0♀			
	4♂	0♀			
Maternal syphilis			4	4	8
Maternal syphilis, not neurosyphilis	3♂	1♀			
Congenital syphilis in siblings	0♂	1♀			
Maternal dementia paralytica	1♂	2♀			
	4♂	4♀			
Paternal syphilis			6	2	8
Paternal syphilis, not neurosyphilis	2♂	1♀			
Paternal dementia paralytica	4♂	1♀			
	6♂	2♀			
Congenital syphilis in siblings (paternal and maternal syphilis absent or unknown)			3	1	4
Dementia paralytica in relative (uncle) and no other data			1	0	1
No data on syphilis in any member of family			18	12	30
Total number of cases with mental disease in immediate family			36	19	55

juvenile dementia paralytica in which mental disease occurred in some member of the family. In most instances the incidence of mental disease was a matter of historical data and not subject to verification on the part of the examiner. Consequently it is not possible to state whether or not some of the reported cases of mental illness were instances of syphilis. In most reports it was merely stated that the persons were "insane."

These 55 cases represent 13.7 per cent of the 399 cases in which the family history was given and 8.4 per cent of the total of 653 cases. These figures are both very high as contrasted to the incidence of mental disease (as indicated by the number of resident patients in state hospitals) in the average population, which is roughly about 0.004 per cent (about 400 in each 100,000 of population).

The incidence of mental disease in the family in these cases and its association with syphilis in other members of the family are shown in table 11. The significance of this high incidence of mental disease in the families of patients with juvenile dementia paralytica cannot be stated. It may support the theory of *erbliche Belastung* as applied to dementia paralytica by Naecke,[40] Raymond[41] and Schüle[42] and to juvenile dementia paralytica by Alzheimer[43] and Coquerelle.[44] On the other hand, Schmidt-Kraepelin[45] could find no evidence in her cases that this "burdening with hereditary traits" is of any significance in the development of juvenile dementia paralytica. She believed that it is no more pronounced than in the cases of adults with dementia paralytica, while Kalb (quoted by Schmidt-Kraepelin), on the basis of exhaustive studies, stated that there existed no influence of special hereditary impairments. On the other hand, Ameline[12] believed that heredity played a part in the transmission of adult dementia paralytica and found 7 cases in a series of 238 in which following dementia paralytica in the first generation the malady developed in a member of the second generation (and the syphilis was probably not congenital).

In regard to the influence of heredity it seems incorrect to compare the juvenile type and the acquired type of dementia paralytica. In the congenital cases one must consider the damaging effect of syphilis on the germ plasm (the parasyphilis of Fournier) together with the family inheritance, while in the acquired form only the family inheritance plays a part. The high incidence of mental disease in the family in this large series of cases of juvenile dementia paralytica certainly suggests the existence of a predisposition to vulnerability of the central nervous system.

SUMMARY AND CONCLUSIONS

1. In the entire series of 653 cases of juvenile dementia paralytica the presence of syphilis clinically or serologically (or both) was established in one or more members of the family in 369 instances (56.5 per cent).

---

40. Naecke, P.: Der endogene Faktor in der Pathogenese der Paralyse, Ztschr. f. d. ges. Neurol. u. Psychiat. **18**:280, 1913.

41. Raymond, F.: Etudes de pathologie nerveuse. Maladies familiales, Paris, H. Delavue, 1910.

42. Schüle, H.: Statistische Ergebnisse aus 100 Fällen von progressiver Paralyse, Jahrb. f. Psychiat. u. Neurol. **22**:18, 1902.

43. Alzheimer: Die Frühform der allgemeinen progressiven Paralyse, Allg. Ztschr. f. Psychiat. **52**:533, 1895.

44. Coquerelle, A.: Contribution à l'étude des rapports de la paralysie générale juvénile et de l'hérédosyphilis, Thèse de Paris, 1922.

45. Schmidt-Kraepelin, T.: Ueber die juvenile Paralyse, Monographien aus dem Gesamtegebiete der Neurologie und Psychiatrie, no. 20, Berlin, Julius Springer, 1920.

2. While maternal syphilis is known to be present in every instance in which there is a congenitally syphilitic offspring, it was demonstrated as present in 223 cases. Syphilis was manifest as neurosyphilis in 26 per cent of the 223 cases of maternal syphilis, as compared to 6.4 per cent, the incidence of clinical neurosyphilis in women (in the clinic of the Johns Hopkins Hospital). Thus mothers of patients with juvenile dementia paralytica show nearly four times the frequency of clinical neurosyphilis exhibited in average groups of syphilitic women.

3. Maternal neurosyphilis in cases of juvenile dementia paralytica is about equally distributed between dementia paralytica and other clinical types of neurosyphilis.

4. Paternal syphilis was demonstrated in 226 cases, of which 35.4 per cent were cases of neurosyphilis. The average incidence of clinical neurosyphilis in males is 20.38 per cent (clinic of the Johns Hopkins Hospital), which indicates that the fathers of patients with juvenile dementia paralytica show nearly twice the incidence of clinical neurosyphilis present in average groups of syphilitic men.

5. Dementia paralytica in the father occurred twice as frequently as all other forms of neurosyphilis (57 with dementia paralytica and 23 with other types) and in these cases the patient was male in 49 cases and female in 25 cases. These findings suggest the predisposition for paternal transmission of dementia paralytica.

6. Both parents were demonstrated to have syphilis in 72 cases (11 per cent), and in these 72 cases neurosyphilis was present in one or both parents in 29 instances (40.3 per cent).

7. Neurosyphilis was demonstrated in some member of the family (other than the patient) in 143 instances, or 22.5 per cent of the 653 cases surveyed, a figure nearly twice as large as that for the average incidence of clinical neurosyphilis. Dementia paralytica occurred in 14.7 per cent of the cases, which is three times the average incidence of that disease.

8. Dementia paralytica was present in the mothers of 20 males and of 10 female patients with juvenile dementia paralytica. It was present in the fathers of 34 male and of 23 female patients. It was present in both parents in 6 instances, the patient being male in each case. Such findings do not substantiate the transmission of dementia paralytica through the same sex.

9. Dementia paralytica was present in a brother or sister of the patient in 17 instances.

10. Several instances of neurosyphilis in three generations of a family are cited, furnishing further clinical evidence for familial predisposition to neurosyphilis.

11. The high incidence of neurosyphilis (36.8 per cent), the high percentage of dementia paralytica in the parents (14.7 per cent), the numerous instances of two or more siblings with neurosyphilis and the presence of neurosyphilis in three generations all lend clinical support to the theory of a neurotropic strain of S. pallida but might equally well support the theory of a familial predisposition to neurosyphilis.

12. Mental disease occurred in one or more nonsyphilitic members of the family in 55 instances. This high incidence of mental disease supports the theory of *erbliche Belastung* of the earlier German writers as well as of many others that juvenile dementia paralytica occurs frequently in a "degenerate" family stock.

TOXEMIA OF PREGNANCY

ITS RELATION TO CARDIOVASCULAR AND RENAL DISEASE; CLINICAL AND NECROPSY OBSERVATIONS WITH A LONG FOLLOW-UP

W. W. HERRICK, M.D.
AND
ALVIN J. B. TILLMAN, M.D.
NEW YORK

This article on toxemia of pregnancy is based on the study of this condition at the Sloane Hospital for Women during the past fifteen years. Nine hundred and thirty cases have been observed, 594 of which have been followed up in at least semiannual examination by the medical rather than by the obstetric attending staff. The object of the study has been to find out what type of woman is subject to the condition during pregnancy and what pathologic changes are present not only at the time of the toxemia but in the years following. Of importance also are the life expectancy of these patients, the cause of death and the observations at necropsy.

Our observations suggested that the toxemias may not be isolated, idiopathic states but that they are possibly related to certain common general medical conditions. That this suspicion may have some foundation is suggested by important statistical figures. Of the 594 women followed up for an average period of five and six-tenths years, with extremes of one year and twenty-two years, 90, or 15.7 per cent, have died. This figure becomes 2.7 per cent if calculated on the basis of the death rate in the general female population between the ages of 20 and 45 years, which is 0.4 per cent. In other words, the mortality rate in the group studied is almost seven times the average death rate for women of child-bearing age. Of the 90 deaths, 72, or 80 per cent, were from causes within the cardiovasculorenal field. This observation fits in with impressions gained from the clinical follow-up studies, namely, that the victim of toxemia of pregnancy is peculiarly liable to such serious sequelae as nephritis and hypertensive cardiovascular disease. This was pointed out by Corwin and one of us (W. W. Herrick), who before the Association of American Physicians in 1927 reported a clinical study of 239 cases in which nephritis was present in 64, or 26.7 per cent, and hypertensive cardiovascular disease in 175, or 73.2 per cent, of the patients followed up from six months to six years after the toxemia.

Read at the Forty-Ninth Session of the Association of American Physicians, Atlantic City, May 1934.

From Sloane Hospital for Women and the Departments of Obstetrics and Gynecology and Internal Medicine, Columbia University.

One of the chief difficulties in the follow-up study of patients with these conditions, and perhaps the dominant occasion for this report, is the lack of logical classification of the toxemias and particularly of their sequelae. In most obstetric clinics a woman with high blood pressure is classified as having nephritis. Primary vascular disease with hypertension is still unrecognized. The differential diagnosis of primary nephritis and primary hypertensive cardiovascular disease need not be discussed here. It is true that the clinical differentiation is not always possible, especially in the end-stages. A pathologist, however, differentiates with more assurance.

From our studies we are convinced that the thread of one of these two conditions runs through at least a majority of the instances of toxemia. We believe that it is generally possible and highly important to separate these threads during gestation and in the follow-up period because of the difference in prognosis for both the mother and the child and the difference in suitable management of the mother.

The contrasting clinical pictures of the toxemias related to primary nephritis and those related to hypertensive cardiovascular disease may be set forth best by describing what happens when pregnancy takes place in a woman already afflicted with either malady.

In the case of established nephritis, whether latent or manifest, pregnancy activates and aggravates roughly in proportion to the size of the fetus. In other words, serious manifestations usually occur late in the period of gestation. The dominant sign of nephritis is albuminuria. In nephritis complicating pregnancy this is marked and persistent. Hypertension may or may not be present, but often appears after the onset of albuminuria or not until the later phases of the disease. There is a tendency to retention of nitrogen, to an albuminuric type of retinitis, to anemia and to edema, to early death of the fetus in about 60 per cent of the cases, and in more serious instances to uremia, occasionally with convulsions. With death of the fetus or with delivery the symptoms may or may not clear away promptly. In the follow-up period, however, the majority of patients reveal persistent albuminuria and often hypertension, retinitis and other evidences of nephritis. The life expectancy is relatively short, and death from uremia or infection is the rule. Should reproduction again be attempted, the renal breakdown appears earlier in pregnancy and is usually more serious, and the result is less likely to be a living child. In a woman with nephritis, repeated pregnancy seems to encroach further on the factor of safety of the kidney and should be avoided.

If pregnancy takes place in a woman who is subject to hypertensive cardiovascular disease, however mild, a quite different series of events may be expected in the average case. As gestation advances the diastolic as well as the systolic blood pressure tends to rise. Usually no distur-

bance other than the hypertension is noted either by the physician or by the patient until the blood pressure reaches 180 systolic and from 110 to 120 diastolic. Rather abruptly at this point a slight or pronounced albuminuria, often of varied amount, may appear. If the condition progresses, a decline in the renal output, and edema, may follow. To this may be added evidence of hepatic degeneration in epigastric pain and tenderness, perhaps with icterus. Changes in mentality may be noted, exaggerated deep reflexes may appear and typical eclampsia with convulsions may take place. The retinal picture is important. The arteries at first are small and spastic and may constrict the veins. Hemorrhages may occur. In case of eclampsia diffuse edema is often added, and retinal separation with a fairly good prognosis as to vision may be seen. Patches of white exudate are not frequently seen. In contrast to the nephritic group, there is no retention of urea nitrogen in the blood. The uric acid content of the blood may be increased.

This process may be rapid in its development, as in acute eclampsia, or may be slow, extending over a period of many weeks; it may be arrested at any stage, some of the milder cases showing only a moderate rise in blood pressure with or without slight and variable albuminuria.

In the cases of eclampsia in our series (70) the immediate maternal mortality was 17.1 per cent; during the follow-up period 22.5 per cent of the survivors died. The immediate fetal mortality was 60.9 per cent. In the milder, nonconvulsive cases the maternal deaths were few and the fetal mortality was not over 15 per cent. If albuminuria and edema can be controlled, cases with moderate hypertension, especially those in which it appears late in pregnancy, can usually be carried on to viability of the fetus or to term.

The behavior of this type of patient in future pregnancies is variable. Eclampsia recurred in 14.3 per cent of the 70 patients, but an appreciable percentage of women with eclampsia in later pregnancies present a mild disturbance marked by hypertension. For example, Corwin and Herrick cited a consecutive series of 154 multiparas with toxemia, 13 per cent of whom gave a history of convulsions in previous pregnancies. In the patients of this group without a history of convulsions the same observers found a recurrence of hypertension in 96 per cent showing a tendency to higher ranges in later pregnancies in the majority.

The clinical follow-up study of the patients with toxemia marked by hypertension as the dominant feature with albuminuria secondary and subsidiary appeared to reveal the stigmas of hypertensive cardiovascular disease rather than those of primary nephritis, that is, in patients who had enduring sequelae of toxemia. At the end of the first year of follow-up about 30 per cent revealed a blood pressure above 150. After the third year this state was observed in over 50 per cent. More than 50 per cent revealed some degree of sclerotic change

in the retinal arteries. Albuminuria was variable but was present in some amount, however small, in about 20 per cent. Cardiac enlargement and thickening of the larger palpable arteries were common. Edema was rare. Most of the women in the group were large of frame and obese and were more inclined to plethora than to anemia. We classified the patients showing sequelae of this kind in the follow-up period in the group with hypertensive cardiovascular disease rather than in that with primary nephritis. In the group with cardiovascular disease the common causes of death were cardiac failure and apoplexy. In a few instances uremia dominated the final picture, presumably the consequence of renal arteriosclerosis.

While the clinical evidence of the existence of these two types of disturbance in association with or following toxic pregnancy is suggestive, the evidence from the necropsies seems almost conclusive. Thus far in our series of cases with a long follow-up period 11 necropsies have been performed by competent pathologists. These examinations have been made without the knowledge on the part of the pathologist that any special interest was attached to the subjects. One examination was made in the hospital of the Rockefeller Institute and the rest in the Presbyterian Hospital. The necropsy observations corroborated the clinical observations. Two distinct types of cases were described by the pathologist. In 4 cases the postmortem diagnosis of primary glomerulonephritis was made, and in 7, that of primary cardiovascular disease with arteriolosclerosis.

The kidney of the patient with acute eclampsia has frequently been described. It presents a degenerative process showing profound changes in the glomeruli and in the contributory and component vessels with lesser alterations in the tubules. Fahr spoke of this as glomerulonephrosis. Signs of inflammation are absent. The glomeruli are swollen and devoid of blood and exhibit fatty degeneration. There are significant widening and swelling of the walls of the glomerular capillaries and of the afferent arterioles with subsequent hyalinization and secondary tubular atrophy. The process in the glomeruli seems to be one of ischemic necrosis which is the result of narrowing of the vascular channels by swelling of the walls or by spasm. The theory of ischemic necrosis caused by spasm receives some support from the study of the capillaries of the nail fold in cases of eclampsia and particularly from the study of the retina. Spasticity of the retinal arteries is an early feature of the vascular type of toxemia of pregnancy. This is often followed by edema and other forms of retinal degeneration and rarely by separation; in many instances a later development is definite arteriosclerosis.

Few pathologists have studied the eclamptic kidney after a long follow-up period. Bell has described the case of a patient on whom

necropsy was performed seven years after the eclampsia. Although Bell considered that capillary thickening and the hyalinization of the glomeruli were evidence of a peculiar kind of disease of the kidney, he stated that "the findings, including cardiac hypertrophy, suggest that the patient must have had hypertension."

The changes in the renal structure found by Bell seem to differ in no essential particular from those in our 3 cases of eclampsia with more detailed clinical study. The changes were considered by members of the department of pathology of the Presbyterian Hospital to be characteristic of the end-stage of cardiovascular disease with hypertension. In 1 case the renal lesions were very slight, the principal changes being in the arteries of the spleen, pancreas, suprarenal glands and liver. It is of no small significance that in the remaining 4 of the 7 cases, which were examples of nonconvulsive and milder types of vascular toxemia and which we considered to be nonnephritic, verifying observations were made both in the clinical follow-up and at autopsy. This is further evidence of a fact that has been shown repeatedly: that the necropsy observations in cases of nonconvulsive, preeclamptic and milder types of toxemia are identical with those in cases of eclampsia.

The clinical and pathologic evidence suggests a continuous chain of events in cases of toxemia with cardiovascular sequelae. The vascular damage of the acute phase of the disease may not be repaired but may become permanent, leading in at least half the cases to the manifestations of hyperpiesis in the follow-up period and to ultimate disclosure at autopsy of characteristics of this generalized disease of the arterial system which ends in cardiac failure, apoplexy or renal failure through narrowing of the vascular channels supplying the kidneys.

SUMMARY

A group of 594 cases of toxemia of pregnancy has been studied by internists during the period of toxic gestation and during a follow-up period averaging five and six-tenths years, with extremes of one and twenty-two years. The death rate in this group was 2.7 per cent, based on the mortality figures for women in general between the ages of 20 and 45 years in the city of New York, which is 0.4 per cent. The mortality in this group, without reference to the comparative death rate in the average female population, was 15.7 per cent. Of the deaths among 594 cases followed up, 80 per cent were from causes within the cardiovasculorenal field.

From a medical point of view the cases fall into two groups: The first, and smaller, is associated with a latent or manifest primary glomerulonephritis, and the second, and larger, with hypertensive cardiovascular disease. These differ in their clinical manifestations during the toxemia and in the follow-up period and also in the prognosis and

treatment. More than one-half the survivors of toxic pregnancy reveal symptoms and signs of one or the other of these conditions within three years.

Among the 594 cases 11 have come to necropsy. In these the pathologists, independently of the clinic, have described two types of disease: In 4 cases there were changes typical of chronic glomerulonephritis, and in 7, changes characteristic of cardiovascular disease with hypertension.

It seems probable that the pathologic changes characteristic of eclampsia, preeclampsia and other vascular types of toxemia are not transitory but in over 50 per cent of the cases are permanent, merging into those of chronic vascular disease as disclosed in this group at necropsy.

REPORT OF CASES AND NECROPSY OBSERVATIONS

The hypertensive group comprises 7 cases.

CASE 1.—*History.*—E. L., aged 28, an American, was a multipara. The personal and family history gave no evidence of cardiovasculorenal disease or of infection. The patient was in good health until six years before death, when the first pregnancy occurred. The blood pressure and urine were normal at the third month, but in the seventh month there was edema with high blood pressure and convulsions. Cesarean section was performed, with death of the infant. The patient was well for the next four years, but the blood pressure remained high and albuminuria persisted. Two years before the final admission to the hospital the patient became pregnant, and a therapeutic abortion was done because of edema and vomiting. One year later retinal hemorrhage was observed, and shortly afterward the following observations were made: blood pressure, 260 systolic and 150 diastolic; albuminuria; retinitis; arteriosclerosis; cardiac hypertrophy; uriniferous breath; output of phenolsulphonphthalein, 19 per cent, and blood urea, 0.92 mg. per hundred cubic centimeters. The patient did fairly well until just before the final admission, when edema, insomnia, headache and dyspnea increased. She appeared to be chronically ill. The retina revealed papilledema, evidence of recent and old hemorrhages, patches of exudate and marked tortuosity of the retinal arteries. The heart was enlarged and showed gallop rhythm with an apical systolic murmur. Hydrothorax and considerable pulmonary moisture were present. The liver was enlarged, and there was well marked edema of the legs. The preliminary diagnosis was advanced cardiovasculorenal disease following toxemia of pregnancy six years before.

Laboratory Examination.—There was marked secondary anemia, with an increased blood urea content, which reached a maximum of 1.79 Gm. per liter. The urine showed a high trace of albumin with a few granular casts. The specific gravity was never above 1.012, and the output of phenolsulphonphthalein was 10 per cent after two hours.

Course.—Bilateral hydrothorax increased; the progress continued steadily downward, and the patient died on Oct. 13, 1932, with a picture of circulatory failure with pulmonary edema. The clinical diagnosis was chronic glomerular nephritis; chronic uremia; cardiac hypertrophy and insufficiency; bilateral hydrothorax; advanced albuminuric retinitis, and hypertension.

Gross Observations at Necropsy.—There was moderate edema of the ankles, and large amounts of fluid were present in the peritoneal cavity and in both thoracic cavities. The heart weighed 500 Gm. The endocardium showed superficial hemorrhages. There was some edema of the leaflets of the mitral valve and hemorrhage was observed in the anterior papillary muscle. Plaques around the openings of both coronary arteries somewhat occluded that of the left artery. The myocardium of the left ventricle was enormously thickened, and that of the right moderately so. There was no fibrosis. Except for a few plaques, which did not cause occlusion, the coronary arteries were normal. The aorta showed a few atheromatous patches. The lungs were edematous. The spleen, liver, pancreas and suprarenal glands were normal. The brain showed moderate subpial edema. The walls of the basal vessels showed no thickening but some yellow atheromatous patches.

Kidneys.—The kidneys weighed 60 Gm. each and were practically identical. The capsules stripped fairly easily, leaving a granular surface consisting of grayish-red nodules from 1 to 1.5 mm. in diameter, with brownish-red tissue between. The cortex measured from 2 to 4 mm. in thickness. The normal striations were not very distinct. In the cortex no glomeruli could be made out. The renal vessels were prominent.

Microscopic Observations at Necropsy.—The muscle fibers of the heart were hypertrophied. The intima of the aorta was thickened in several places by increased connective tissue, usually hyalinized close to the muscularis. There was some infiltration by round cells with small hemorrhages, and small scars were present about the nutrient vessels. These areas displayed broken and frayed elastic fibers; some of the arterioles showed thickened walls and some were completely occluded. The walls of the smaller vessels of the spleen and pancreas were thickened and hyalinized almost to complete occlusion of the lumen, and the larger vessels showed plaques of intimal thickening. There were similar, though less marked, changes in the suprarenal arteries. The pituitary gland was normal.

Kidneys: Under the low power lens the section appeared to be a succession of dilated tubules separated by new and old scars, with little normal renal tissue. Some of the glomeruli were completely hyalinized, but most of them were large, and instead of the normal delicate papillary tufts they contained a mass of cells enmeshed in more or less hyaline material which was often adherent to the edge of the capsule. The capsule in several of the glomeruli was enormously thickened. No crescents were seen. Many of the convoluted tubules were widely dilated, and their cells were desquamated. The terminal tubules were filled with granular casts and were often completely desquamated. A few of them contained polymorphonuclear cells with pinkish coagulum. The interstitial tissue was infiltrated by round cells. The connective tissue was greatly increased, and in it were found areas of atrophied tubules. The smaller branches of the arterioles had thick walls which occasionally were hyalinized, many being completely occluded by their hyalinized walls. Sometimes the vessels entering glomeruli, or even the glomeruli themselves, were occluded by hyaline material. The elastic tissue was reduplicated in certain of the arterioles with a sharp band lacking in elastic tissue. In other arterioles there was a diffuse increase in elastic tissue throughout the thickened wall. In a few arterioles all the elastic tissue appeared to be absent. The elastic tissue in the larger vessels was normal. A considerable number of fine fibers were to be found in the glomerular capsule and in the connective tissue between the tubules.

Anatomic Diagnosis.—This was: generalized arteriosclerosis; advanced arteriolonephrosclerosis; myocardial hypertrophy; chronic passive congestion of the lungs and spleen; bilateral hydrothorax; ascites; edema of the extremities; early bilateral lobular pneumonia; encephalomalacia of the left frontal lobe and the cerebellum, and ulcer of the stomach.

Summary.—This was a case of hypertensive disease in a woman under 30 with extreme renal atrophy and characteristic arteriolar changes in the kidneys, the spleen, the suprarenal glands and the aorta. The symptoms were known to date back at least six years to her first pregnancy, which ended in eclampsia.

Case 2.—*History.*—C. M., aged 45, an Irish multipara, was admitted to the hospital on May 26, 1931, and died on May 30. The last pregnancy, four years before admission, was marked by dyspnea and edema, but no records of the blood pressure were available. She learned of her high blood pressure two years later, at which time there developed vertigo, orthopnea, palpitation and paresthesia of the right leg. She was hospitalized, and phlebotomy was performed with beneficial results. She improved gradually, but another pregnancy occurred with immediate aggravation of all the symptoms. There were increasing edema, precordial pain, nausea, epistaxis and hemoptysis.

Physical Examination.—There were marked orthopnea, cyanosis and edema of the face and the extremities. The retinas revealed papilledema, narrow pale arteries and constriction of the veins but no hemorrhage or exudate. The heart was hypertrophied, but there were no murmurs. Slight pulmonary edema was observed. The blood pressure was 240 systolic and 160 diastolic, and the pulse rate was 110 and regular. The reflexes were normal.

Laboratory Examination.—The specific gravity of the urine varied between 1.016 and 1.027; there was a high trace of albumin and the urine contained granular and waxy casts.

Course.—The course was progressively downward. The nonprotein nitrogen content rose from 35 mg. per hundred cubic centimeters on admission to 64 mg. three days later. Retinal hemorrhages developed. There was a sudden rise in temperature followed by coma and death.

The clinical diagnosis was: pregnancy between the fifth and sixth month; chronic cardiovascular disease (hypertensive) aggravated by pregnancy; cardiac hypertrophy with failure and impending pulmonary edema; arteriosclerosis, and possible terminal cerebral hemorrhage.

Gross Observations at Necropsy.—The heart was enlarged, weighing 520 Gm. The aortic leaflets were thickened and slightly fused. There was no obvious fibrosis of the myocardium, but there were two hemorrhages near the tip of the anterior papillary muscle. In the anterior descending branch of the left coronary artery and in the circumflex branch were sclerotic intimal plaques. One of those in the left branch was large; it narrowed the lumen, and in the fixed preparation a small reddish plug, suggestive of a thrombus, almost completely occluded the lumen. Numerous small, soft, yellowish plaques were present in the aorta and in the great vessels of the neck.

Kidneys: The right kidney weighed 200 Gm., and the left, 140 Gm., and the two were practically identical. The capsule stripped easily, and the surface was smooth except over a few old depressed scars at the nutrient vessels. The cortex, which was well differentiated from the medulla, was from 4 to 5 mm. thick and appeared to be slightly paler than normal. The stellate veins were prominent. The striations were distinct. The pyramids were deep red and in sharp contrast to the cortex. The renal arteries did not show much sclerosis.

Microscopic Observations at Necropsy.—The lumen of the coronary arteries was constricted owing to a thickening of the intima. The blood vessels of the spleen had greatly thickened hyaline walls, some being practically obliterated. About the portal spaces a large number of hepatic cells had become necrotic, and much hemorrhage was present. The arteries in some of these spaces had thickened walls and were somewhat hyalinized, but no thrombosed vessels or syncytial cells were seen. There was nuclear fragmentation in these areas. In some places the entire lobule was hemorrhagic and necrotic, and no normal hepatic cells could be seen. In others there was only a small area of necrosis about a portal vein. The blood vessels of the pancreas did not appear to have thickened walls. The intima of the basilar artery was markedly thickened, somewhat homogeneous and vacuolated and contained some cellular and nuclear débris, lymphocytes and mononuclears, fibroblasts and lipoid-containing cells. The media and adventitia showed no abnormalities.

Kidneys: The glomeruli were relatively avascular, and some appeared to be more fibrotic than usual. Few of them, however, were adherent to Bowman's capsule. A number of blood vessels had thickened walls and some appeared to be hyalinized. A few contained hyaline thrombi. The epithelium lining the tubules was fragmented, and a number of purplish-staining concretions were seen in the tubules. The tissue between the tubules appeared somewhat congested. The pelvis of the kidney appeared normal. An elastic tissue stain showed some small blood vessels to have thickened walls, which was evidence more of muscular hypertrophy than of sclerosis.

Anatomic Diagnosis.—This was: moderate generalized arteriosclerosis; cardiac hypertrophy; fibrosis of the myocardium; infarct of the papillary muscle of the left ventricle; necrosis of the liver, with eclampsia; hemorrhage into the mucosa of the colon and urinary bladder, and arteriosclerotic scars of the kidney.

Summary.—This was a case of a woman of 45 in whom hypertension was aggravated during her fifth pregnancy to the point of cardiac failure. From the clinical point of view death appears to have been the result of failing circulation, and anatomically the coronary, the splenic and the large cerebral vessels seem to have been the only ones which were definitely sclerotic. The pancreatic and renal arterioles were practically unaffected. The most important feature of the case was the presence of eclampsia-like hemorrhages in the substance of the liver.

The presence of lesions similar to those of eclampsia in the liver of a patient dying of heart failure following hypertensive cardiovascular disease with a history of toxemia of pregnancy four years previously is of special interest. The possible vascular basis of such lesions and their relation to the circulatory disease later found in over 50 per cent of examples of eclampsia and preeclampsia deserve notice.

CASE 3.—*History.*—M. M., aged 29, an American multipara, was admitted to the hospital on Aug. 28, 1930, and died on September 11. The patient had quinsy in 1924, and albumin was found in the urine in the course of an examination for life insurance in 1919. She had been married for four and a half years, but there were no symptoms until the sudden onset of eclampsia three years before death in the seventh month of her first pregnancy. No antepartum blood pressure readings or urinary findings were recorded. A forced delivery was made at the New York Nursery and Child's Hospital, but the blood pressure did not decline afterward. During the follow-up, gradual improvement appeared to take place, but hypertension, headache, palpitation and occasional edema continued. A year before

admission to the Presbyterian Hospital the patient again became pregnant and experienced a spontaneous miscarriage in the third month at the Flushing Hospital. Subsequently she felt fairly well until two weeks before admission to the hospital, when her vision became impaired and there was accompanying headache with frequent dyspnea, palpitation, vomiting and diarrhea.

Physical Examination.—The patient presented a pale and pasty appearance. Retinal examination revealed blurring of the optic disks, narrowing of the vessels, arteriovenous compression and patches of pigmented scarring which suggested former hemorrhages. The breath was ammoniacal. The heart was enlarged and revealed gallop rhythm and a loud and ringing aortic second sound. The blood pressure was 230 systolic and 145 diastolic. The clinical diagnosis was: chronic nephritis, hypertension, arteriosclerosis, uremia and well marked secondary anemia.

Laboratory Examination.—The examination revealed: hemoglobin, 52 per cent; erythrocytes, 3,200,000; blood urea, 1.03 Gm. per liter, and creatinine, 0.6 Gm. per liter. The patient became more restless and irrational, with bilateral choking of the optic disks and a pericardial friction sound. The blood urea rose to 2.25 Gm. per liter. The urine showed a trace of albumin in all specimens, with the specific gravity never over 1.010. The patient died with hyperpyrexia.

Gross Observations at Necropsy.—The heart weighed 340 Gm. The left ventricle was hypertrophied, and the endocardium was thickened. Both coronary arteries showed atheromatous plaques without encroachment on the lumen. In the aorta were small raised atheromatous plaques. The lungs showed bronchopneumonia at the bases.

Kidneys: The right kidney weighed 50 Gm., and the left, 40 Gm., and the two were practically identical. The capsule stripped easily and revealed a surface covered with pale tan nodules between 1 and 2 mm. in diameter, with dark red depressed areas between them. The whole surface of the kidney, both nodules and internodular spaces, was covered with minute transparent spots just large enough to be seen. On section, the cortex was seen to be narrowed and made up of tan colored nodules measuring from 1 to 2 mm. with dark red internodular tissue. The whole surface was covered with minute depressions like pinpricks, corresponding to the transparent spots on the surface. The pyramids appeared normal.

Microscopic Observations at Necropsy.—The muscle fibers of the heart were hypertrophied, and a majority showed striking vacuolation. The intima of the aorta showed thickening with irregular fibrous tissue. There was no fragmentation of elastic tissue. One branch of the coronary arteries showed thickening of the intima. The central arteries of the spleen showed hyaline changes.

Kidneys: The kidneys were fairly well marked out with radial alternating bands of contrasting structure. The first and most striking was composed of tortuous and tremendously dilated convoluted tubules running from or near the surface of the kidney to varying depths in the medulla. There was no increase of connective tissue between the loops. The alternating bands were narrower and contained connective tissue, blood vessels, tubules and most of the glomeruli. The connective tissue was moderately abundant and loose. It was infiltrated in varying degrees with round cells. In small areas the cellular infiltration was dense, giving the appearance of small abscesses, but there were no polymorphonuclears. Most of the blood vessels were engorged. Many of the arterioles had greatly thickened walls, almost occluding their lumens. The tubules were either not dilated or only moderately so and were predominantly of the type with low cells and dark-staining nuclei. Some contained hyaline plugs. The number of glomeruli appeared to be decreased. Many were partly or completely hyalinized, and some were adherent

to the capsule, the epithelium of which had overgrown their tufts. There was pink-staining material in some of the capsules. There was no typical crescent formation.

Anatomic Diagnosis.—This was: arteriosclerotic atrophy of the kidneys; mild generalized arteriosclerosis; cardiac hypertrophy; fatty heart; myocardial fibrosis, and lobular pneumonia.

Summary.—This was a case of long-standing hypertensive disease apparently antedating several pregnancies. Although the history of repeated infections of the throat and the age suggested chronic glomerular nephritis, the renal lesions were those of arteriolosclerosis and atrophy. There was little to indicate old inflammatory changes in the glomeruli. There was ulcerative colitis which was probably uremic.

The history suggests underlying nephritis. Without the report of the pathologist it would be difficult for the clinician to classify this case, which might well be of mixed type. Our studies thus far, however, indicate that in most patients with a history of eclampsia there eventually develops arteriosclerosis with or without arteriosclerotic nephrosclerosis rather than what may strictly be called nephritis.

CASE 4.—*History.*—M. S., aged 46, an Italian-American, had ten pregnancies. The first eight deliveries occurred at home. The first ended in stillbirth, the seventh in miscarriage and the tenth in missed abortion. The ninth delivery was at the Sloane Hospital for Women in 1924 and was normal. The patient then was 39. During the antepartum period the blood pressure rose three times to 135 systolic. Otherwise nothing of significance was recorded. In the follow-up clinic, in May 1925, six months after she was discharged, the blood pressure was observed to be 210 systolic and 110 diastolic. There was complaint of nausea, cough, vomiting and occasional blurring of vision. At this time the patient was stout, florid and cyanotic. A year and a half later, in December 1926, she was again hospitalized for threatened abortion in her tenth and last pregnancy. At this time her blood pressure was 190 systolic and 112 diastolic; it subsided rapidly to 120 systolic and 76 diastolic after curettage. Retention of nitrogen was not present. The urine showed a very faint trace of albumin. Five years later, in January 1931, she was admitted to the Presbyterian Hospital because of high blood pressure, vertigo, dyspnea and cough.

Physical Examination.—She presented the picture of circulatory failure and of pulmonary infection. There were cyanosis, dypsnea, edema and evidence of bronchopneumonia at the bases of the lungs. The heart was enlarged, with a mitral murmur. The blood pressure was 200 systolic and 100 diastolic. The urine showed a trace of albumin and granular casts.

The patient died five days after admission.

The clinical diagnosis was bronchopneumonia with cardiac insufficiency, arterial hypertension and chronic nephritis.

Gross Observations at Necropsy.—There was a moderate bilateral blood-tinged pleural exudate. The heart was enormously enlarged, weighing 760 Gm. The leaflets of the mitral and tricuspid valves were thickened along the line of closure. The endocardium of the left ventricle was thickened and opaque over the papillary muscles and beneath the aortic valve. The coronary arteries showed slight yellow and gray thickening of the intima. The intima of the abdominal aorta showed numerous yellow and gray plaques. The lungs showed bilateral bronchopneumonia.

The pulmonary vessels had numerous yellow and gray intimal plaques. The spleen had prominent blood vessels. The lobulations of the liver were distinct and presented as dark brown areas surrounded by grayish-yellow bands. On section the parenchyma had a nutmeg appearance with large red central zones surrounded by yellowish-gray portal areas. Occasional yellow round areas about 1 cm. or more in diameter were seen. The parenchyma of the pancreas appeared to be yellowish pink, spotted with tiny glistening points.

Kidneys: The organs resembled each other. The right kidney weighed 170 Gm., and the left, 160 Gm. The capsule stripped with difficulty and left a gray granular surface in which were several large depressed scars. The striations were not obliterated. The glomeruli stood out as tiny specks the size of a pinpoint. The pyramids had distinct radiations and congested vessels. The arcuate arteries were rather prominent.

Microscopic Observations at Necropsy.—The intima of the aorta was thickened and hyalinized in its inner portion; the elastic tissue fibers were increased in number and many were fragmented. A branch of the aorta showed a thickened intima in which were many delicate elastic tissue fibers. The arterioles of the lung had a slightly thickened intima, and those of the spleen were strikingly thickened, at times by hyalinization and again by laminated and vacuolated tissue, but mainly they showed a grayish-yellow swelling of the intima which extended through the wall of the vessel. The smaller arteries of the spleen had thickened and hyalinized intima. The capsule of the liver was thickened, and the lobulations were destroyed. In and about the central areas was considerable congestion, with disappearance by atrophy of the hepatic cells. The portal areas had an increased amount of connective tissue. The lymphatic vessels were prominent. The arterioles showed changes similar to, but not as advanced as, those in the spleen. The capsule of the left suprarenal gland was thickened. The small arteries had hypertrophied muscle cells and slightly thickened intima with occasional hyaline degeneration. In the right suprarenal gland only small masses of lipoid-containing cortical tissue surrounded by thick layers of dense fibrous connective tissue were found embedded in a loose connective tissue stroma which was infiltrated by lymphoid and wandering cells. By the Moeller method (fixation and decalcification) a section showed purple-staining calcified masses embedded in connective tissue. The arterioles and small arteries had thickened and hyalinized intima. There was no medullary tissue.

The capillaries of the ovary were engorged, and the small arteries had thickened and hyalinized intima. In the pancreas some increase in interlobular tissue was found. The arterioles showed changes similar to those seen in the spleen. The capillaries were engorged. The arterioles of the stomach had thickened intima, and there were some hyaline deposits in the lymphoid areas.

Kidneys: A pink granular or fibrinous precipitate was present in many of the glomerular spaces. One glomerulus showed adhesion with its capsule and a focal hyalinization of several loops which was covered by proliferating epithelium of the capsule and tuft. The arteriole of this tuft was thickened and hyalinized, and a short distance from it was a similar vessel the lumen of which was obliterated. Most of the arterioles were like this one and showed an increase of connective tissue in the intima. The tubules contained hyaline, granular and epithelial cell casts. The small arteries had thickened intima, and several had obliterated lumens. The capillaries were engorged.

Anatomic Diagnosis.—This was: arteriolosclerosis of the kidneys, spleen, pancreas, stomach and liver; generalized arteriosclerosis; cardiac hypertrophy and

dilatation; fibrosis of the myocardium; confluent bronchopneumonia; atelectasis; hydrothorax; chronic congestion of the lungs, liver, spleen, pancreas and kidneys; fibrosis and calcification of the right suprarenal gland, and fibrous peritoneal adhesions.

Summary.—This was a case of hypertension which was known to have existed for three years, with marked cardiac hypertrophy and characteristic arteriolar changes in the spleen, pancreas, kidneys and stomach. The patient died of intercurrent bronchopneumonia, and although there was histologic evidence of early lesions in the kidney there was no clinical evidence of renal insufficiency.

CASE 5.—*History.*—A. M., aged 47 years, German-American, was a multipara. Four children were living and well. The patient had had four miscarriages. All the deliveries except the last occurred at home. No record of the blood pressure or of the urinary findings was obtainable. The personal history was irrelevant until 1924 when she was treated for hypertension and nephritis at the Harlem Hospital. The patient was first admitted to the Sloane Hospital for Women on July 14, 1925, as presenting an emergency case. She was in the seventh month of pregnancy and had hypertension, enlargement of the heart, vascular and possible albuminuric retinitis and edema of the face and ankles. The blood pressure was 210 systolic and 136 diastolic. An examination of the blood revealed no retention of nitrogen. The urine contained from 10 to 18 per cent of urinary albumin by volume, and acetone, diacetic acid and finely granular casts. On July 23 there was induced delivery of a premature living baby. The patient was discharged on August 26 with the blood pressure 212 systolic and 164 diastolic and albumin in the urine varying from a faint to a high trace. The Wassermann reaction of the blood was positive. During the follow-up period the patient complained of headache, vertigo and dyspnea, and edema was present. Marked sclerosis of the retinal vessels was noted. There was serious caries with infected gums. Cardiac hypertrophy was present, and the blood pressure was 220 systolic and 160 diastolic. She received antisyphilitic treatment throughout 1930 and 1931. In January 1930 she had a brief attack of aphonia and hemiplegia. She was admitted to the Presbyterian Hospital on Sept. 28, 1931, with an aggravation of the previous symptoms.

Laboratory Examination.—The blood urea was 0.42 and the creatinine 0.24 Gm. per liter. There was a faint trace of albumin in the urine as well as a few hyaline and granular casts. The blood pressure was 238 systolic and 140 diastolic.

The patient became restless, irrational and incontinent and died suddenly on October 6.

The clinical diagnosis was: hypertension; cardiac hypertrophy and insufficiency; chronic myocarditis; general arteriosclerosis; syphilis; dental caries; external hemorrhoids, and varicose veins of the internal saphenous system.

Gross Observations at Necropsy.—The left pleural cavity contained 1,500 cc. of dark red fluid and clotted blood; the right cavity contained 50 cc. of clear lemon-colored fluid, and a similar amount filled the pericardial sac. The heart weighed 780 Gm. The larger coronary arteries appeared to be tortuous. In general the endocardium was normal. The left ventricle was markedly dilated. There was a little thickening of the endocardium over the septum with subendocardial hemorrhages. The coronary arteries were not narrowed, although atheromatous plaques were scattered along the larger branches. The mediastinal connective tissue about the aorta was filled with a dark red clot of recent origin and enclosed the aorta and esophagus and bulged into the left pleural cavity. The aorta presented many gray and yellow atheromatous plaques. These were especially marked about the arterial ostia; a few were superficially ulcerated. The intima was wrinkled. A crescent-shaped

slitlike opening through the intima and media was present on the posterior wall of the aorta beneath the orifice of the ductus arteriosus. In this zone the media split readily. The splenic artery along the body of the pancreas was unusually tortuous and presented yellow atheromatous plaques. The pancreas was somewhat atrophied.

Kidneys: The left kidney weighed 140 Gm., and the right, 150 Gm. The capsule stripped easily, leaving an irregular, coarsely nodular surface in which stellate vessels were conspicuous. There was an occasional thin-walled cyst filled with clear lemon-yellow fluid. There were small irregular, shallow depressions on the outer surface. On section, a narrowed cortex was seen which averaged from 4 to 5 mm. across. The cortical markings were somewhat obscure, but the glomeruli stood out as conspicuous bright red dots. The medulla, except for congestion, appeared to be normal. The main renal artery was not unusual.

Microscopic Observations at Necropsy.—The fibers of the heart muscle were hypertrophied and frequently contained vacuoles. There was some slight replacement fibrosis. The intima of the aorta was slightly and uniformly thickened. The media was unusually thick and contained many nuclei. The aorta presented no evidence of syphilis. The main lesion in the aorta consisted of areas of nuclear depletion. In other areas there was definite and striking hypertrophy of the muscle with irregular splits at times extending across the media in steplike fashion. The elastic tissue was markedly fragmented, beaded and disarranged in some sections. The lung showed an occasional thick-walled arteriole, and the splenic arterioles were thick-walled. In the pancreas many of the arterioles were thick-walled and some were completely obliterated.

Kidneys: Several narrow linear zones were present in the cortex in which there was a small excess of connective tissue. The tubules in these areas were usually lined with basophilic cells having large, vesicular, deeply-staining nuclei. There were also present in these areas completely obliterated hyalinized glomeruli. There was often a small amount of lymphocytic reaction in the scarred areas. The small arterioles were partly obliterated by an intimal proliferation of connective tissue. Eosinophilic material was often seen outside the intima. Some of the smaller arteries showed a similar change.

Anatomic Diagnosis.—This was: generalized arteriosclerosis; arteriolosclerosis of the spleen, kidneys and pancreas; cardiac hypertrophy and dilatation, and dissecting aneurysm of the aorta.

Summary.—This was a case of a woman who was admitted twice to the hospital with hypertension as the essential clinical finding, together with cardiac hypertrophy and albumin and casts in the urine. The Wassermann reaction was positive. Death was sudden. The essential observations at autopsy were: mild arteriosclerosis; arteriolosclerosis involving especially the kidneys; cardiac hypertrophy, and rupture of the aorta at the isthmus with the formation of a dissecting aneurysm.

Case 6.—*History.*—E. B., aged 42, a Negress, was a multipara. She was last admitted to the hospital on Feb. 11, 1933, and died on February 22. In 1918 the patient had an uncomplicated, precipitate delivery of a living infant at the Sloane Hospital for Women. Later in the same year there was a miscarriage followed by curettage. In 1919 a forceps delivery of a living child at home was accompanied by hemorrhage. There was a miscarriage in 1922, and in 1924 a normal delivery occurred at the Sloane Hospital for Women, at which time syphilitic changes in the placenta were recorded. The maximum blood pressure at this time was 126 systolic and 90 diastolic. There was a trace of albumin in the urine ranging from faint to high. In 1925, in the follow-up, a heavy trace of albumin

was found. In the same year there was a spontaneous miscarriage followed by curettage. In the following year the blood pressure was 156 systolic and 110 diastolic, a faint trace of albumin was found in the urine, and there was definite retinal arteriosclerosis. In 1928 a normal delivery occurred at the Sloane Hospital for Women. During the pregnancy there was no rise of the blood pressure above the normal and no albumin was present until just before delivery when there was a high trace. In the follow-up clinic in 1929 an examination revealed a blood pressure of 214 systolic and 118 diastolic and an evident increase in the arteriosclerotic changes. In the same clinic in May 1930 the patient complained of headache and vertigo. The retinas revealed marked vascular changes. At that time there was a faint trace of albumin in the urine, and the blood pressure was from 180 to 200 systolic, and 130 diastolic. The patient was obese. In December 1930 the patient was again pregnant. In the sixth month the blood pressure was 200 systolic and 104 diastolic. A faint trace of albumin was present in the urine. Headache, nausea and vomiting were among the symptoms. Supravaginal hysterectomy was performed, and two months later the patient was free from symptoms, the blood pressure being 130 systolic and 80 diastolic. One month later there was a return of palpitation and headache. The blood pressure was 240 systolic and 126 diastolic. The retinal vessels showed sclerosis; there were marked cardiac hypertrophy, a soft systolic murmur and an accentuated aortic second sound. Antisyphilitic treatment was begun on April 1, 1931, because of two weakly positive, and in spite of several negative, Wassermann reactions. In June 1932 there was severe headache. The blood pressure was 230 systolic and 150 diastolic. In February 1933 weakness was increased to the point where housework was impossible. Nausea, vomiting, dyspnea, orthopnea and one attack of acute mania occurred. The maximum blood pressure was 265 systolic and 145 diastolic. The retinas showed flame-shaped hemorrhages with marked narrowing of the retinal vessels and arteriovenous constriction. The heart was enlarged, with gallop rhythm and an accentuated aortic second sound. There was edema of the ankles and legs and moderate anemia. The nonprotein nitrogen content of the blood rose to 100 mg. per liter. A trace of albumin was found in the urine, which had a specific gravity of 1.017. The electrocardiogram revealed evidence of myocardial damage. There developed a pericardial friction rub, and the patient died in a state of uremia on February 22.

Gross Observations at Necropsy.—The heart weighed 480 Gm. There was serofibrinous pleurisy. The cavities of the heart seemed dilated. There was patchy thickening of the endocardium with a few subendocardial hemorrhages. The myocardium of the left ventricle was thickened. There was a beginning fusion of the aortic cusps at the commissures. The papillary muscles were hypertrophied. The coronary arteries showed small yellow intimal plaques, and the aorta, a few, small, slightly raised intimal plaques. In the spleen the vessels stood out prominently. The brain revealed no changes.

Kidneys: The two organs were identical, the left weighing 130 Gm., and the right, 190 Gm. The capsule stripped easily, exposing a diffusely granular surface on which there were innumerable small, slightly raised, yellowish areas and many small areas of hemorrhage ranging from the size of a pinpoint to several millimeters in diameter. Fetal lobulations were present. In many areas the boundary between the cortex and the medulla was no longer distinct. Numerous small, irregular yellowish areas and small areas of hemorrhage were seen on the cut surface. Two distinct kidney pelves were present in each kidney; both were injected, and small hemorrhages were seen in the mucosa of each. Two ununited ureters were also present in each kidney.

Microscopic Observations at Necropsy.—The myocardial fibers were hypertrophied. A few of the small branches of the coronary vessels showed intimal thickening, and one was obliterated. The intima of the aorta was thickened by fibrous connective tissue, some of which appeared to be hyalinized. The muscular coats of a moderate-sized artery of the adventitia were atrophic and revealed some thickening of the intima. The internal elastic coats were reduplicated and in some areas showed fragmentation. Calcium was not present. The walls of the central arterioles of the spleen were markedly thickened and hyalinized. Many of the lumens were completely obliterated. The internal elastic lamella of many of the central arterioles was straightened, reduplicated and fragmented. In a few of the small vessels only small fragments of elastic tissue remained. There was intimal thickening of the arterioles of the portal areas of the liver. The pancreas showed atrophy of some of the acini and revealed fibrous replacement with marked increase of the interlobular tissue. There were marked thickening and hyalinization of the walls of the arterioles, many of which were completely occluded and some of which contained a few dark blue granules, probably calcium. In some of the arterioles, particularly those which were completely occluded, very little elastic tissue remained. In others the internal elastica was straightened, reduplicated and fragmented. In the larger vessels the changes were not marked. The increased fibrous tissue was well marked.

Kidneys: The small and medium-sized arteries showed considerable intimal thickening, and most of the arterioles, including those entering the glomeruli, showed marked thickening of their walls with hyalinization and partial or complete occlusion of the lumens. Some of the necrotic arterioles were infiltrated with polymorphonuclear and mononuclear cells and contained cellular débris. No normal-appearing arterioles were seen. A few essentially normal glomeruli were seen, but most of them showed from moderate to markedly advanced changes. Comparatively few completely hyalinized or collapsed glomeruli were seen. The glomeruli showed a variety of lesions: hemorrhage, congestion and hyalinization. The arteries showed straightening, fragmentation and occasional reduplication of the internal elastica. In many of the occluded arterioles practically no elastic tissue remained.

The suprarenal glands showed moderate thickening of the arteriolar walls in the connective tissue outside the capsule. The cortical cells appeared to contain an abundant amount of lipoid. The capillaries were congested. Several of the arterioles in the deep portion of the cortex were completely occluded by hyalinized fibrous tissue. In a few of the arterioles outside the capsule the internal elastica was fragmented. In most of them it appeared to be normal, however, and the thickening of the wall involved chiefly the middle coat. In the occluded arterioles of the cortex no elastic tissue remained.

Anatomic Diagnosis.—This was: generalized arteriosclerosis; arteriolar nephrosclerosis; cardiac hypertrophy and dilatation; clinical uremia; calcium deposits in the lungs; slight arteriosclerosis of the aorta; fibrosis of the myocardium; acute fibrinous pericarditis; chronic passive congestion of the liver, lungs and spleen, and fibrous peritoneal adhesions.

Summary.—This was the case of a Negress who had many pregnancies and miscarriages and a long history of hypertension. She was probably syphilitic. She died in a uremic state, with cardiac failure. The arteriolar lesions were of the acute necrotizing type and were especially well shown in the kidneys, the pancreas, the spleen and the suprarenal glands. In the kidneys there was moderate secondary atrophy, and in the pancreas there was diffuse fibrosis, probably

as a result of the arterial change. The coronary vessels seemed to have been spared, and the myocardium showed little change other than hypertrophy. The renal lesions, on closer study, gave the impression of a more complex change than that due merely to the vascular disease. We are inclined to associate the tubular changes with the effects of the intensive antisyphilitic treatment. The hypophysis, in the single section examined, showed definite proportional decrease of the oxyphil cells and an increase in the basophil element similar to the change described in cases of hypertension by Krause. Another interesting feature was the extensive calcification of the pulmonary veins and alveolar septums.

CASE 7.—*History.*—C. D., aged 67, an American, was admitted to the hospital on Oct. 17, 1933, and died on October 20. The patient was admitted because of a swelling in the right lower quadrant of the abdomen with dull pain, which had been present for several weeks. There was a history of scarlet fever at the age of 10 years, followed by cardiac disturbance and deafness. During the few years prior to admission dyspnea and palpitation on exertion, occasional edema of the ankles and high blood pressure had been noted. The patient was married in 1893 and had five pregnancies. The first and fourth resulted in stillbirth at term and the fifth in a spontaneous abortion. Eclampsia occurred with the first pregnancy in 1896.

Physical Examination.—The patient was a feeble, poorly nourished woman of 67. Bilateral deafness was present. The left side of the heart was enlarged, and there were forceful impulse, systolic shock and a short systolic murmur at the apex. The rate was irregular from premature contractions. The blood pressure was 170 systolic and 95 diastolic. There was an evident mass in the right lower quadrant of the abdomen. Pretibial edema was present. The cell count and the nonprotein nitrogen content of the blood were normal. Two days after admission the patient was found aphasic and dyspneic with a fibrillating heart. Death which occurred an hour later was thought to be due either to cerebral accident or to heart failure.

The clinical diagnosis was: right ovarian cyst; chronic cardiovascular disease; mitral stenosis and insufficiency, and cerebral hemorrhage.

Gross Observations at Necropsy.—A large cyst containing 4,000 cc. of cloudy yellowish fluid was found in the right ovary. The heart weighed 330 Gm. There was thickening of the mitral valve with a few vegetations near the line of closure. The cusps of the aortic valve were slightly adherent at the commissures. Small yellowish atheromatous patches were found in the ascending aorta. The left coronary artery showed several arteriosclerotic patches. The lungs revealed nothing significant, and no abnormalities were noted in the arteries of the spleen, liver, pancreas or suprarenal glands.

Kidneys: The kidneys were identical. Each weighed 150 Gm. The surface was nodular. The remains of fetal lobulations were seen, and in addition there were rather large scars and a number of cysts. The capsule stripped with difficulty and pulled away a little of the kidney tissue with it, leaving a finely granular surface with a number of cysts and some irregular scars. The cortex was reduced in size. The glomeruli could be seen, but the striations were indistinct. The blood vessels were slightly sclerotic.

The brain was not examined.

Microscopic Observations at Necropsy.—There was slight thickening of the mitral valve, which had become hyalinized and at one point calcified. There was some polymorphonuclear infiltration. The media of the aorta showed rarefaction, vacuolation and degeneration of the nuclei. The adventitia was normal. The lungs were moderately congested. The spleen showed no change, and the suprarenal glands and the pancreas were normal.

Kidneys: The kidneys showed small cortical scars containing atrophied tubules and sometimes hyalinized glomeruli. No glomerular adhesions were present. The blood vessels showed thickened walls.

Anatomic Diagnosis.—This was: arteriosclerosis of the aorta; senile arteriosclerosis; patent foramen ovale; acute endocarditis—chorda tendineae of the mitral valve; cystadenoma of the right ovary; tuberculosis of the bronchial lymph nodes; miliary tuberculosis of the liver; infarcts of the lungs and phleboliths of the spleen and the accessory spleen.

Summary.—The valvular lesions are not significant. The patient may have died of a cerebral accident, but this could not be verified.

It is possible that senile arteriosclerosis accounts for this picture entirely. The previous eclampsia cannot, however, be ignored as a possible contributory factor in the vascular changes.

The nephritic group comprises 4 cases.

Case 8.—*History.*—R. R., aged 28, an American-born Jewess, was a primipara. She was first observed in the outpatient department of the Sloane Hospital for Women on Dec. 24, 1924, in the early weeks of pregnancy. Scarlet fever, diphtheria and an injury to the spine which caused lateral curvature were experienced in childhood.

The blood pressure was normal. The urine was of low specific gravity and showed a heavy trace of albumin. On June 5, 1925, the blood pressure had risen to 150 systolic and 112 diastolic. On this account the patient was admitted to the ward. Here she presented no evidence of infection and none of cardiovascular disease. Albuminuria persisted, suggesting an underlying renal lesion. Several admissions to the hospital followed during the subsequent six months because of persistent albuminuria and occasional hypertension. She was delivered of a normal infant on June 10, 1925. In the follow-up, in 1926, there was complaint of weakness. A physical examination revealed blood pressure of 136 systolic and 90 diastolic and some sclerosis of the larger vessels and edema of the ankle. Albuminuria persisted. In 1928 the edema increased. The albumin was 20 per cent by volume, and many finely and coarsely granular casts were present. The blood pressure was 146 systolic and 110 diastolic. The patient was admitted to the hospital of the Rockefeller Institute several times, where in May 1930 the blood pressure was noted to be 218 systolic and 132 diastolic. Secondary anemia was present, and there were purpuric spots on the extremities. There was marked retention of nitrogen. Albumin, blood and casts were present in the urine. In May 1931, on the final admission to the last-mentioned hospital, there was complaint of blindness. Serious albuminuric retinitis was found. The blood pressure was 260 systolic and 164 diastolic. The excretion of phenolsulphonphthalein was but a faint trace in two hours. The test for urea clearance showed a result about 6 per cent of normal. Death occurred from uremia on June 15.

The clinical diagnosis was: chronic nephritis; cardiac hypertrophy and uremia.

Gross Observations at Necropsy.—The heart weighed 400 Gm., but otherwise it was normal. The spleen, liver, pancreas and suprarenal glands were normal. The left kidney weighed 100 Gm., and the right, 150 Gm. The capsules of the kidneys did not evert when cut and were stripped off with difficulty, leaving a granular surface. The cortex averaged about 4 mm. in thickness.

Microscopic Observations at Necropsy.—Kidneys: Sections stained with eosin and methylene blue showed marked distortion of the renal architecture. The

glomeruli just beneath the capsule were as a rule normal except that they were enlarged. The glomeruli farther in showed all the variations of destruction. Practically all showed one or more adhesions between the capsular and the glomerular epithelium. The connective tissue forming the capsule was increased in thickness. Some glomeruli were almost completely hyalinized, leaving only a few nuclei visible; others showed a few capillary loops remaining. The tubules varied. Some were increased in size owing to hypertrophy of the cells lining the tubules, others were atrophied, many contained hyaline casts, and many contained the shadowy outlines of red blood cells. Some tubules were completely obliterated by scar tissue. The blood vessels were engorged with red blood cells. A few of the larger arteries showed some thickening of the media. Sections showed a wrinkled basement membrane in the glomerulus and around the tubules. Numerous masses partly of intercapillary fibers were seen. Many of the glomerular loops were compressed by this means and also by an increase in the endothelial cells.

Anatomic Diagnosis.—This was: chronic nephritis; cardiac hypertrophy; acute bronchitis and generalized anasarca.

Summary.—This was the case of a woman under 30 in whom nephritis was discovered first during pregnancy. This might have been of scarlatinal or of diphtheritic origin. In spite of persistent albuminuria and mild hypertension pregnancy was successfully terminated. During a follow-up period of six years there was a gradual increase in symptoms of renal insufficiency, and the patient died of uremia. Gross and microscopic observations revealed evidence of chronic nephritis.

Case 9.—*History.*—E. K., aged 37, an American, was a primipara. Renal disturbance was discovered at the age of 17 after several attacks of sore throat. During the sixth month of her first and only pregnancy, in 1921, without previous symptoms, coma occurred suddenly with convulsions. Abortion was induced. After an interval of five years without symptoms headache, nausea, vomiting and visual disturbances appeared with a rise in the blood pressure and retention of nitrogen. After a variable course there was an infection of the respiratory tract followed by generalized edema, dyspnea and blurring of vision. She was first admitted to the hospital on Jan. 3, 1929, and was discharged improved on January 20, was readmitted on May 23 and died suddenly on May 28.

Physical Examination.—The heart was enlarged. The blood pressure was 250 systolic and 140 diastolic. Ecchymoses were present over the surface of the skin. The fundi revealed arteriosclerosis with fresh hemorrhages. There was marked anemia, and urine of low specific gravity showed a high trace of albumin and casts. General anasarca and signs of pericarditis developed before death. The clinical diagnosis was: chronic nephritis; uremia; hypertension; cardiac hypertrophy, and serofibrinous pericarditis.

Gross Observations at Necropsy.—The heart weighed 450 Gm. The pericardium was covered with shaggy fibrinous exudate in which were small hemorrhages.

Kidneys: The left kidney weighed 150 Gm., and the right, 160 Gm. The capsule stripped with difficulty, leaving a pebbly surface. On the cut surface it was difficult to distinguish between the cortex and the medulla; where the distinction was possible the cortex was not more than 2 mm. thick. The markings on the cut surface were irregular. There were a few punctate hemorrhages. The blood vessels on the cut surface were not prominent.

Microscopic Observations at Necropsy.—The capsule was thickened and torn. Beneath it were several small scars. The glomeruli showed various stages of

degeneration, some with only slightly thickened capsules or adherent tufts, some completely hyalinized and others atrophied. Hyaline changes had occurred in some of the intraglomerular capillaries. The tubules varied greatly in size; polymorphonuclears were present in some. The interstitial tissue was increased and contained small collections of lymphocytes. The smaller vessels had slightly thickened walls. The elastic laminae of the vessels were reduplicated.

Anatomic Diagnosis.—This was: chronic intracapillary glomerulonephritis; cardiac hypertrophy; acute organizing fibrinous pericarditis; bilateral hydrothorax; acute congestion of the spleen and the liver; patent foramen ovale; general mild arteriosclerosis, and moderately advanced sclerosis of the coronary arteries.

Summary.—This was a case of chronic glomerulonephritis of the intracapillary type with terminal pericarditis in a woman with a history of a convulsive pregnancy twelve years before.

Case 16.—*History.*—G. S., aged 38, an American, was a primipara. She was admitted to the hospital Jan. 22, 1931, because of persistent hypertension, albuminuria and retention of nitrogen. There was a history of scarlet fever and pneumonia in early life. In 1928, in the fifth month of her only pregnancy, evidence of renal difficulty was discovered. The blood pressure was 170 systolic and 90 diastolic. Edema of the back and lower extremities was present. The urine contained a large amount of albumin, and the nonprotein nitrogen content of the blood was slightly elevated. A stillborn child was delivered, after which the patient was hospitalized because of pyelitis. The anasarca vanished. The blood pressure fell to 118 systolic and 90 disastolic. Ten days after discharge the blood pressure was 154 systolic and 90 diastolic. Albuminuria persisted, and the urine was of low specific gravity. The eyegrounds were normal. Gradually moderate secondary anemia developed, and the nonprotein nitrogen level rose to 114 mg. per hundred cubic centimeters of blood. In January 1931 the patient was emaciated and pale. There was moderate general arteriosclerosis. The retinal arteries were small, and several minute white patches were noted. The patient was discharged unimproved at her own request on February 1, and was readmitted on June 26 because of orthopnea, dyspnea, cough, epistaxis, nausea, vomiting and palpitation following a "cold."

Physical Examination.—The blood pressure was 170 systolic and 100 diastolic. General anasarca, uremic breath and a pericardial friction rub were noted. The hemoglobin content was 32 per cent, and the red blood cells numbered 1,700,000. The blood urea was 40.7 mg., and the creatinine, 7.5 mg. per hundred cubic centimeters.

The patient died on July 31.

The clinical diagnosis was: chronic nephritis; uremia; hypertension; secondary anemia, and pericarditis.

Gross Observations at Necropsy.—All the serous cavities showed exudate. The heart was enlarged and weighed 420 Gm. The epicardium was roughened and thickened. The coronary arteries showed some yellow plaques without occlusion. Atheromatous plaques were present in the aorta. The liver, spleen, pancreas and suprarenal glands were normal.

Kidneys: The left kidney weighed 30 Gm., and the right, 15 Gm. The capsule stripped with difficulty, leaving a pale, rough granular surface. The cortex was from 3 to 4 mm. wide, and a few glomeruli were visible. An unusual number of large arteries were visible in the cortex. The pyramids were comparatively large. The striations were seen with difficulty and were for the most part regular.

The pelvis was of normal size and presented a pale mucosa which was studded with minute yellow cysts and a few petechial hemorrhages. The peripelvic fat was increased. The right kidney was similar to the left; the cortex was smaller, measuring from 1 to 2 mm. in width. In a few instances the pyramids were absent and the calices extended to the capsule. No glomeruli were visible.

Microscopic Observations at Necropsy.—The cortex bore numerous completely hyalinized glomeruli. Other glomeruli showed only partial hyalinization with adhesion of various loops to Bowman's capsule. Their tufts were large and there appeared to be an increased amount of connective tissue binding several contiguous loops together. A few unaffected glomeruli remained near the periphery. Many of the tubules had disappeared and were replaced by connective tissue. These areas were near the completely hyalinized glomeruli. The majority of the remaining tubules were grouped in islands associated with the glomeruli which were still functioning. They were dilated and lined by low cuboidal or flattened epithelium. Their lumens were filled with pink granular material, and hyaline and granular casts plugged some of the smaller tubules. When the dilated tubules were near the surface they projected considerably above its level. The stroma was greatly increased and was highly cellular, the cells being chiefly small round cells. The arterial walls were markedly thickened. There was a pronounced increase in the amount of elastic tissue of the walls of the smaller arteries. In another section few glomeruli were seen, but those present were large, with hypertrophied tufts and only occasional hyalinization of a loop. There was less stroma throughout the section, the tubules being present in larger numbers, dilated and tortuous. Near the pelvis was congestion of the capillaries, and a few of the tubules were completely plugged with polymorphonuclear leukocytes. They were found in the interstitial tissue in one isolated clump associated with small round cells and slight edema.

Summary.—This was a case of chronic glomerulonephritis with uremia and hypertension. One of the sections of the kidney showed acute pyelonephritis which was probably fatal. The pericarditis was probably due to the uremia.

CASE 11.—*History.*—L. Z., aged 29 years, German, was a primipara. Her history was irrelevant until the onset of the first pregnancy, which was marked by early vomiting and headache. On March 3, 1931, in the fourth month of pregnancy, the patient was admitted to the hospital as presenting an emergency case.

Physical Examination.—There were marked edema of the face and notable cardiac enlargement. The blood pressure was 180 systolic and 90 diastolic. There was moderate enlargement of the liver. The urine contained a heavy trace of albumin and numerous casts. The nonprotein nitrogen content of the blood was 82 mg. per hundred cubic centimeters; the uric acid 12.5 mg., and the creatinine 6.4 mg.

On March 26 the fetus was delivered by vaginal hysterotomy. This did not influence the condition. There were increasing retention of nitrogen in the blood and the other evidences of progressing uremia. The patient died on April 2.

The clinical diagnosis was: chronic nephritis; hypertension; cardiac hypertrophy, and acute uremia.

Gross Observations at Necropsy.—The heart weighed 385 Gm. There were a few yellow plaques in the aorta. The spleen, pancreas, liver and suprarenal glands were normal. The left kidney weighed 190 Gm., and the right, 210 Gm. The right kidney showed a double ureter and pelvis. The capsule was somewhat adherent, and the surface was pale and granular. The cortex was decreased in thickness and showed old scars.

Microscopic Observations at Necropsy.—The blood vessels of the heart were normal. The lungs revealed edema. The sinuses of the spleen were engorged and small hemorrhages were present. The liver was congested but was otherwise normal. The kidneys showed large scars alternating with columns of dilated tubules. In the scars were many fibrotic glomeruli, numerous small lymphocytes and atrophic tubules. Other glomeruli were enlarged and showed numerous adhesions to the capsule of Bowman. In many the capillary loops were obliterated. Many others were in a process of fibrosis, showing adhesions and thick obliterated capillaries. Some tubules were dilated, and some were lined with fragmented columnar cells. A few contained a homogeneous brownish-staining plug which was acellular. There were several large abscesses infiltrated with polymorphonuclear leukocytes and fibrinous material. The tubules in these areas contained many red blood cells. About the pelvis was marked infiltration with lymphocytes and plasma cells. The vessels were sclerotic. The arterioles in another section showed markedly thickened walls.

Anatomic Diagnosis.—This was: subacute glomerulonephritis; cardiac hypertrophy; a puerperal uterus and retained placenta; pulmonary edema, with partial atelectasis of the lungs; abscesses of the kidney; fibrous pleural adhesions; hemosiderosis of the spleen, and congenital malformation of the kidney.

Summary.—This was a case of subacute glomerulonephritis, the etiology of which was not indicated in the history. With pregnancy there was apparently an exacerbation of a renal lesion which necessitated the termination of the pregnancy. In spite of abortion the symptoms of renal insufficiency continued. The patient died after seven days. There was also a superimposed interstitial inflammation, probably bacterial.

OXYGEN UTILIZATION AND LACTIC ACID PRODUCTION IN THE EXTREMITIES DURING REST AND EXERCISE

IN SUBJECTS WITH NORMAL AND IN THOSE WITH DISEASED CARDIOVASCULAR SYSTEMS

SOMA WEISS, M.D.
AND
LAURENCE B. ELLIS, M.D.
BOSTON

Adequate information as to the state of the peripheral circulation in health and in various stages of heart disease is lacking. Some investigators [1] still consider that the behavior of the peripheral circulation is entirely dependent on the action of the heart, and that disturbances of this circulation can be regarded as an index of an early stage of heart failure. Eppinger and his co-workers,[2] on the other hand, have claimed that primary changes in the peripheral circulation precipitate failure of the diseased heart. Still other workers have presented evidence indicating that the early clinical manifestations of failure depend, as a rule, on changes in the pulmonary circulation due to cardiac insufficiency. In certain types of heart disease with primary failure of the left ventricle, such as arterial hypertension, arteriosclerosis and aortic insufficiency, a severe degree of disability may be present, with marked alteration in the hemodynamics of the pulmonary circulation but with a normal or only slightly altered peripheral circulation.[3]

From the Thorndike Memorial Laboratory, Second and Fourth Medical Service (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1. Lewis, T.: Early Signs of Cardiac Failure of the Congestive Type, Brit. M. J. **1**:849, 1930; Diseases of the Heart, New York, The Macmillan Company, 1933.

2. Eppinger, H.; Kisch, F., and Schwarz, H.: Das Versagen des Kreislaufes, Berlin, Julius Springer, 1927.

3. (*a*) Weiss, S.: Circulatory Adjustments in Heart Disease: A Concept of Circulatory Failure, Ann. Int. Med. **5**:100, 1931. (*b*) Robb, G. P., and Weiss, S.: Effect of Digitalis and Rest on Pulmonary and Peripheral Circulation in Patients with Circulatory Failure Caused by Heart Disease, Proc. Soc. Exper. Biol. & Med. **29**:1231, 1932; Cardiac Asthma (Paroxysmal Cardiac Dyspnea) and the Syndrome of Left Ventricular Failure, J. A. M. A. **100**:1841 (June 10) 1933; The Velocity of Pulmonary and Peripheral Venous Blood Flow and Related Aspects of the Circulation in Cardiovascular Disease: Their Relation to Clinical Types of Circulatory Failure, Am. Heart J. **9**:742 (Aug.) 1934.

PURPOSE OF THE INVESTIGATION

In the present study, information as to the behavior of the peripheral circulation in subjects with normal and in those with diseased cardiovascular systems was sought by studying the utilization of oxygen and the production of lactic acid in the upper and lower extremities during rest, while the subject was standing and after exercise. Provided the metabolism is unchanged, the arteriovenous oxygen difference is an index of the flow of blood through the extremity; that is, a decrease in the arteriovenous difference is due to an increase in the blood flow and vice versa. In heart failure the basal metabolic rate is normal or increased. One can therefore interpret an increased arteriovenous oxygen difference in patients with heart failure as evidence of a decreased flow of blood through the extremities. The close interrelation between the supply of oxygen and the formation of lactic acid and the bearing on it of the blood supply to the muscles is suggested mainly by the work of Hill and his associates.[4] It has been suggested that the capacity of the muscles to eliminate the lactic acid formed during exercise depends on the adequacy of the local circulation.

A simultaneous study of the blood flow of the upper and of the lower extremities is of particular interest, since the amount of tissue in the extremities makes up at least from 30 to 40 per cent of the total body tissue and since the circulation within them represents the blood supply to the most important peripheral structures of the body. During and after walking, therefore, changes in the venous blood of the lower extremities represent metabolic alterations in a considerable bulk of active muscle tissue, while blood obtained simultaneously from the relatively passive arms serves as a control and gives information on the state of the relatively inactive tissue.

As an exercise test, we chose stair climbing. It is a natural activity, which involves mainly the muscles of the lower extremities. Other types of muscular work, including bicycle riding, are performed by persons with varying degrees of skill and not always with the same groups of muscles.

METHOD

The investigative procedure was carried out in the morning, with the subject in the postabsorptive state, as follows: The person rested in the horizontal position, or as nearly horizontal as orthopnea permitted, for at least thirty minutes.

4. (*a*) Hill, A. V.: The Oxidative Removal of Lactic Acid, J. Physiol. **48**: x, 1914. (*b*) Hill, A. V.; Long, C. N. H., and Lupton, H.: Muscular Exercise, Lactic Acid, and the Supply and Utilisation of Oxygen: III, Proc. Roy. Soc., London, s.B **96**:455, 1924. (*c*) Hill, A. V., and Lupton, H.: Muscular Exercise, Lactic Acid and the Supply and Utilization of Oxygen, Quart. J. Med. **16**:135, 1922.

Samples of venous blood were then drawn without stasis, under oil, from an antecubital and a femoral vein. The subject then rose, walked 20 feet (6 meters) to an elevator, was carried down two flights of stairs and then walked slowly up two flights (forty-six steps, each 6½ inches [16.5 cm.] in height), walked 20 feet to the bed and lay down, the total procedure taking about two and one-half minutes. Samples of blood from the antecubital and femoral veins were again drawn simultaneously by two operators, immediately after the subject lay down, again after ten minutes and in the case of the femoral blood after twenty minutes also. A sample of arterial blood was also taken under oil, usually from a femoral artery. The heart rate was counted at the apex while the patient was resting and at half-minute intervals after the exercise. The degree of dyspnea and the effort involved in carrying out the exercise were estimated. The venous pressure during rest was determined by the direct method of Moritz and von Tabora,[5] and the vital capacity of the lungs was determined with a Collins spirometer.

In patients with congestive failure so severe as to make the exercise test inadvisable, samples of blood were taken when the patient was at rest and again after two minutes' standing at ease. The blood during rest was drawn in the usual manner, when the patient was standing erect, from a femoral vein and an antecubital vein, with the arm supported approximately horizontally at the level of the heart.

The samples of blood were analyzed for oxygen and carbon dioxide by the method of Van Slyke and Neill [6] and for lactic acid by the method of Friedemann, Cotonio and Shaffer.[7] Duplicate or triplicate determinations were made on each sample. Some of the results of this investigation were presented in 1931.[8]

MATERIAL

The seventeen control subjects chosen as "normal" persons were ambulatory patients suffering from a variety of minor complaints, but with no detectable abnormality of the cardiovascular system. There were seventeen patients with organic heart disease who showed compensation, i. e., who had no symptoms or signs of congestive failure and who could perform the exercise test without appreciable distress. Sixteen patients with heart disease had "dry" failure. They had no detectable physical signs of congestive failure of the peripheral circulation and were comfortable while at rest, but all of them had dyspnea to a greater or less extent on performing the prescribed exercise. There were seventeen patients with frank congestive failure, the symptoms varying from a few râles at the bases of the lungs or the slightest edema of the ankles to massive anasarca or extreme respiratory distress while at rest.

5. Moritz, F., and von Tabora, D.: Ueber eine Methode, beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, Deutsches Arch. f. klin. Med. **98**:475, 1910.

6. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. **61**:523, 1924.

7. Friedemann, T. E.; Cotonio, M., and Shaffer, P. A.: The Determination of Lactic Acid, J. Biol. Chem. **73**:335, 1927.

8. Weiss, S., and Ellis, L. B.: The Peripheral Circulation in Heart Disease, J. Clin. Investigation **10**:672, 1931.

EXPERIMENTAL RESULTS

Oxygen Content and Arteriovenous Oxygen Difference.—The average levels for oxygen in the femoral veins (during rest) in the patients with compensated cardiac disease and in the "normal" subjects were nearly the same (table 1 and charts 1 and 3). This was also true of the arteriovenous oxygen differences. In the two groups of patients with heart failure, particularly in the group with congestive failure, the oxygen contents were lower and the arteriovenous oxygen differences higher. Chart 1 shows the tendency for the patients with congestive failure to have high oxygen differences.

The values obtained for antecubital venous blood were essentially the same as those obtained for the femoral venous blood. There was a slight tendency for the oxygen differences in the leg to be lower and those in the arm to be higher in the group with compensated cardiac disease than in the normal group, but the average for the arm and leg was nearly the same in the two groups. In the patients with failure, the oxygen contents tended to fall and the oxygen differences to rise.

In every case in all of the groups the oxygen content of the femoral venous blood dropped considerably immediately after exercise, and the arteriovenous oxygen difference correspondingly increased (table 1 and chart 1). The average arteriovenous difference after exercise was somewhat greater in patients with cardiac failure than it was in the other groups. This increase was most definite in the group with congestive failure. A comparison of the ranges of values in chart 1 shows that the values for the group with "dry" failure fall within the same range as those for the normal group, although they average slightly higher. The relative increase in the oxygen difference over the resting values, however, tends to be slightly less in the group with congestive failure than in the normal and compensated groups. This was probably due to the fact that the patients with congestive failure utilized the oxygen from their blood to the fullest extent possible, since the average oxygen content of their femoral venous blood after exercise was only 3.7 volumes per cent, and in three of these patients it reached the extraordinarily low level of 2 volumes per cent or less The lowest oxygen content of the femoral venous blood observed was 1.1 volumes per cent. Obviously, in such patients it was a physical impossibility to increase the oxygen utilization to a greater extent. In all of the groups the femoral venous oxygen had returned to approximately the initial resting value in ten minutes.

The observations on the venous blood drawn from the arm immediately after exercise were similar, in general, to those on the femoral blood. In two cases, however, a control and a patient with "dry" failure, the arteriovenous oxygen difference became less instead of greater.

After standing, the findings in the group of five control subjects and the group of seven patients with congestive failure were similar (table 2). The arteriovenous oxygen difference of the leg increased during the two minute standing period in every case, usually to a marked degree. In every case but one it also increased in the arm, but usually to a less extent than in the leg.

Lactic Acid.—The range of values and the average for the lactic acid when the subjects were at rest were practically the same in all groups (table 1 and charts 2 and 3).

In the normal subjects after exercise, the lactic acid of the venous blood draining the active exercising tissue, i. e., the legs, rose sharply from its preceding average resting level of 13 mg. to 29 mg. per hundred

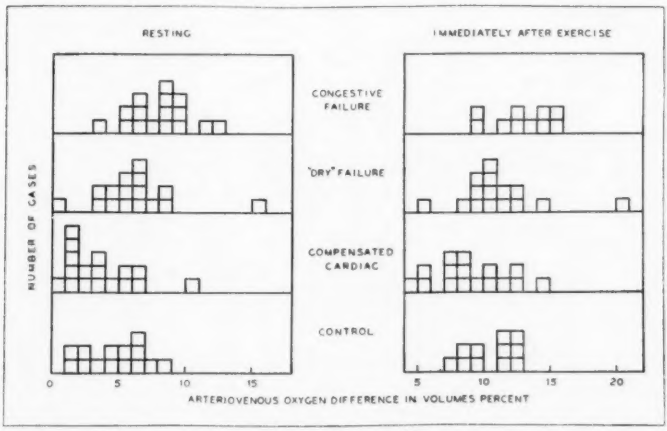

Chart 1.—The distribution curves for the individual cases, showing the femoral arteriovenous oxygen differences during rest and immediately after exercise.

cubic centimeters (table 1 and charts 2 and 3). It then fell rather abruptly in the first ten minutes and more slowly in the succeeding ten minutes, but did not reach the resting value within this time. The general level of the circulating lactic acid, represented by the antecubital venous blood, rose more slowly than that of the lactic acid coming directly from the active tissue of the leg, but in samples taken after the patient had rested for ten minutes the lactic acid of the venous blood was approximately the same in the arm and in the leg.

The lactic acid of the patients with compensated heart disease showed the same changes as did that of the normal subjects. With increasing degrees of cardiac failure, however, there was a distinct tendency for the femoral lactic acid to rise to higher levels immediately after exercise and then to fall at a slower rate than normal (chart 3). This is shown

TABLE 1.—*The Ranges and Averages of Various Values in the Peripheral Circulation at Rest and at Intervals After Exercise in the Normal Subjects and in the Patients with Heart Disease* *

Diagnosis	No. of Cases	Venous Oxygen Content, Vol. per Cent				Arteriovenous Oxygen Difference, Vol. per Cent							Percentage of Saturation of Arterial Blood	Lactic Acid, Mg. per 100 Cc.							Venous Pressure, Cm. of Water	Vital Capacity, Liters
		Leg		Arm		Leg				Arm				Leg				Arm				
		During Rest	Immediately After Exercise	During Rest	Immediately After Exercise	During Rest	After Exercise: Immediately	After Exercise: 10 Min.	After Exercise: 20 Min.	During Rest	After Exercise: Immediately	After Exercise: 10 Min.		During Rest	After Exercise: Immediately	After Exercise: 10 Min.	After Exercise: 20 Min.	During Rest	After Exercise: Immediately	After Exercise: 10 Min.		
Control.....	17	8.1-16.9	4.4-11.7	9.7-16.9	5.1-14.1	1.0-8.8	7.1-12.9	1.5-6.5	.....	1.0-7.9	1.9-12.5	0.8-14.4	86-96	9-16	17-44	15-35	14-23	10-17	13-24	13-23	—2-+10	2.5-5.5
		13.4	**7.3**	**12.9**	**9.5**	**4.7**	**10.3**	**4.0**		**4.7**	**8.3**	**5.2**	**93**	**13**	**29**	**20**	**18**	**13**	**17**	**17**	**+5**	**3.5**
Compensated heart disease	17	6.2-19.6	3.3-15.0	5.6-18.2	2.7-13.9	0.8-10.7	4.1-14.7	1.2-8.9	2.5-7.2	2.4-11.9	4.8-14.0	2.6-11.5	83-99	8-18	19-64	14-40	14-25	9-17	14-31	14-25	—3-+9	2.5-5.1
		14.0	**8.4**	**12.7**	**8.0**	**3.6**	**9.0**	**3.5**	**3.9**	**5.1**	**9.7**	**5.8**	**93**	**12**	**31**	**19**	**18**	**12**	**17**	**18**	**+4**	**3.3**
"Dry" failure..	16	6.9-14.8	3.0-9.9	6.8-15.5	2.6-10.4	0.6-15.5	5.1-21.0	1.4-13.3	1.5-17.7	0.5-10.0	2.8-21.4	2.5-14.1	90-100	9-18	25-66	16-37	13-38	9-20	13-24	14-25	—4-+15	2.0-4.2
		11.6	**6.4**	**11.5**	**6.5**	**6.1**	**11.2**	**4.8**	**5.4**	**6.2**	**11.3**	**8.0**	**93**	**13**	**36**	**23**	**19**	**13**	**18**	**18**	**+6**	**2.3**
Congestive failure	17	4.2-14.6	1.1-7.4	3.8-15.9	1.7-10.5	3.4-12.9	9.7-15.6	1.4-12.5	1.1-10.8	2.7-13.2	4.5-15.0	0.5-14.3	86-98	10-20	24-47	20-38	17-27	9-20	12-38	13-24	+5-+22	0.9-2.8
		8.5	**3.7**	**9.0**	**4.7**	**7.8**	**12.8**	**6.5**	**6.2**	**7.5**	**11.6**	**8.0**	**91**	**14**	**37**	**30**	**22**	**14**	**22**	**18**	**+13**	**1.9**

* The averages appear in bold-faced type.

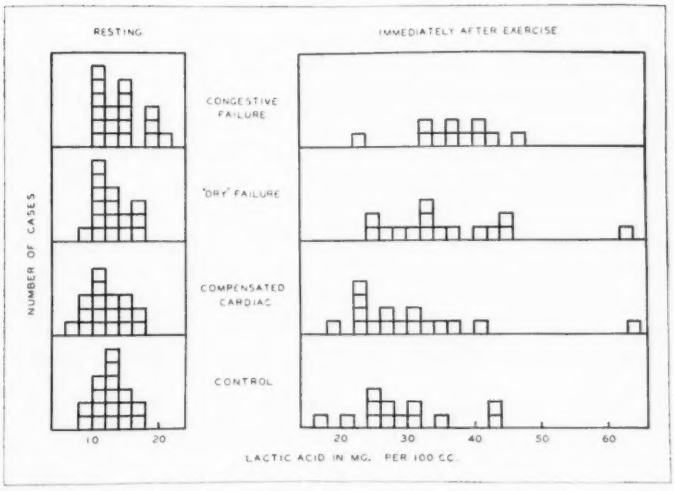

Chart 2.—The distribution curves for the individual cases, showing the femoral lactic acid content during rest and immediately after exercise.

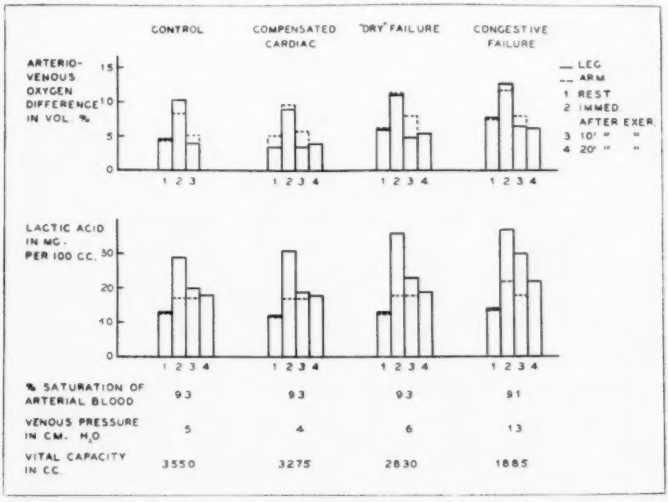
CONTROL
COMPENSATED CARDIAC
"DRY" FAILURE
CONGESTIVE FAILURE
ARTERIO-VENOUS OXYGEN DIFFERENCE IN VOL. %
LEG
ARM
1 REST
2 IMMED. AFTER EXER.
3 10' " "
4 20' " "
LACTIC ACID IN MG. PER 100 CC.
% SATURATION OF ARTERIAL BLOOD 93 93 93 91
VENOUS PRESSURE IN CM. H2O 5 4 6 13
VITAL CAPACITY IN CC. 3550 3275 2830 1885

Chart 3.—The average values in the various groups for the circulatory measurements of the arm and leg during rest and at intervals after exercise.

in the average figures for the groups with "dry" and congestive failure. The upper range of lactic acid values, however, was practically the same in all four groups both immediately and ten minutes after exercise.

Lactic acid determinations were performed on blood from the femoral and antecubital veins taken from five control subjects and six patients with congestive failure while they were erect after standing for two minutes (table 2). The lactic acid values rose on an average of from 1 to 2 mg. above the resting level in both the arm and the leg.

Etiology of the Cardiac Condition and the Response to Exercise.—The arteriovenous oxygen differences and the lactic acid in the leg before and after exercise, grouped according to the type of heart disease, behaved in practically the same manner in the different etiologic types. In certain groups the results are based on too few cases to be of definite significance, but they suggest that the etiology of the heart disease plays

TABLE 2.—*The Effect of Standing on the Arteriovenous Oxygen Difference and the Lactic Acid of Five Normal Subjects and Six Patients with Congestive Failure* *

Diagnosis and Number of Cases	Arteriovenous Oxygen Difference, Vol. per Cent				Lactic Acid, Mg. per 100 Cc.			
	Leg		Arm		Leg		Arm	
	During Rest	After Standing 2 Minutes	During Rest	After Standing 2 Minutes	During Rest	After Standing 2 Minutes	During Rest	After Standing 2 Minutes
Control (5)	2.8-8.8 **5.3**	8.1-11.4 **9.7**	2.6-7.3 **5.5**	2.8-10.1 **7.5**	10.8-16.4 **12.7**	11.3-17.4 **14.3**	9.8-13.0 **11.3**	10.3-13.4 **13.3**
Congestive failure (6)	6.2-9.9 **8.1**	8.2-15.8 **11.2**	3.1-10.5 **6.5**	5.8-12.8 **9.1**	11.5-18.4 **14.3**	12.0-20.6 **15.3**	10.6-18.8 **13.2**	12.6-20.6 **15.4**

* The averages appear in bold-faced type.

little or no part in the nature of the peripheral circulatory response. The exception in our series was a patient with congenital heart disease and "dry" failure. This patient, a man aged 20, with a probable large intraventricular septal defect, showed an unusually high arteriovenous oxygen difference in his femoral blood during rest. This evidence of decreased blood flow was probably due to the intracardiac shunting of blood from the left to the right side and a consequent decrease in the output of blood through the aorta into the peripheral circulation. This patient also showed the highest value for lactic acid in his femoral venous blood after exercise.

Relationship of Edema to the Flow of Blood Through the Legs.—Harrison and Pilcher [9] reported that in the absence of acidosis or intoxication due to digitalis the flow of blood through the edematous extremi-

9. Harrison, T. R., and Pilcher, C.: Studies in Congestive Heart Failure: I. The Effect of Edema on Oxygen Utilization, J. Clin. Investigation **8**:259 (Feb.) 1930.

ties, as measured by the arteriovenous oxygen difference, is increased. Our results did not confirm this. In the one patient with compensated and later with decompensated circulation and with moderate edema of the legs the arteriovenous oxygen difference in the legs during rest rose from 3.1 to 5.8 per cent. The patient, suffering from hypertensive heart disease, showed no evidence of acidosis or of intoxication due to digitalis. The data recorded in table 3 indicate a lack of relationship between the degree of edema and the arteriovenous oxygen difference. Moreover, when the average femoral arteriovenous oxygen differences of the patients showing edema of the legs (table 3) are compared with the

TABLE 3.—*The Relationship Between the Degree of Peripheral Edema and the Arteriovenous Oxygen Difference and Lactic Acid in Seventeen Patients with Congestive Failure*

Case	Degree of Edema	Arteriovenous Difference During Rest, Vol. per Cent		Lactic Acid During Rest, Mg. per 100 Cc.
		Leg	Arm	Leg
1	0	6.0	2.7	13
2	0	9.0	3.1	13
3	0	8.0	8.4	11
4	0	11.0	13.2	15
5	+	8.4	3.1	14
6	+	9.2	10.3	12
7	+	6.0	9.9	10
8	+	5.0	7.5	12
9	+	5.7	5.8	..
10	++	5.8	2.7	19
11	++	8.2	10.5	11
12	++	3.4	6.3	15
13	+++	12.9	11.6	11
14	+++	6.8	5.8	..
15	++++	8.0	7.7	18
16	++++	7.1	9.4	13
17	++++	9.9	8.0	16
Average for normal persons	0	4.7	4.7	13
Average for patients with compensated heart disease	0	3.6	5.1	12
Average for patients with "dry" failure	0	6.1	6.2	13
Average for patients with congestive failure	..	7.8	7.5	14

average values for normal persons, for patients with compensated cardiac disease and for patients with "dry" failure, it is evident that the values in the presence of edema are greater than in any of the other groups. These values, also, are nearly the same as the average values for the arteriovenous oxygen difference in the arm in the same group. This agreement between oxygen differences in the arm and in the leg is similar to that found in the group without edema and is substantial evidence that an increased blood flow in the leg does not exist.

Relationship Between the Lactic Acid and the Oxygen Content of the Venous Blood of the Leg.—The question arose as to whether the high lactic acid values which were obtained could be related to the slow blood flow, causing either anoxemia of the tissues or a deficient removal

of lactic acid from the part where it was formed. This problem cannot be answered with certainty. Some evidence on this point may be gained by comparison of the oxygen content of the femoral venous blood immediately after exercise in patients showing a low lactic acid value (below 25 mg. per hundred cubic centimeters) and in those with high lactic acid (above 35 mg.). Although the patients with the most marked evidence of anoxemia, i. e., oxygen values of 2 volumes per cent or less, showed relatively high lactic acid volume, there were many patients with a high oxygen content and evidence of rapid blood flow who also showed high lactic acid values.

COMMENT

Economic functioning of the circulation depends on the supply to the tissues of an amount of oxygen adequate for the degree of activity of the cells. During work the increased demand for oxygen by a large mass of tissue, such as the lower extremity, is met through a number of functions: an increased cardiac output; a widening of the arteriolar and capillary bed, with a resultant higher capillary blood pressure gradient; an increased degree of utilization of oxygen; and probably also an alteration in the oxidation capacity within the cells. If one or more of these factors become insufficient, the balance of the protoplasm dynamics may become temporarily or permanently disturbed, as manifested particularly by changes in the chemical metabolism. Thus the efficiency of the circulation does not depend solely on the capacity of the heart to increase its pumping function. In normal persons the greatest efficiency of the cardiovascular system is often attained by a good peripheral utilization of oxygen with a relatively slight increase in the work of the heart. The degree of loss of oxygen from the arterial blood in relation to the oxygen consumption of the tissues is therefore one of the best measures of the state of the peripheral circulation.

It has been claimed that the capacity of muscle tissue to resynthesize and oxidize lactic acid in situ is dependent on the effectiveness of the local circulation. Hence the peripheral utilization of oxygen and the escape of lactic acid into the venous blood are supposedly closely related. Determination of the relationship between lactic acid and muscular work in patients with cardiac disease is particularly difficult, because there is no definite agreement regarding this interrelation in health. The rôle of the formation of lactic acid in the contraction of amphibian and mammalian muscle was first demonstrated by Fletcher and Hopkins [10] and was further studied by others, mainly by the school of Meyerhof.[11] Hill, Long and Lupton [4a] found that the blood lactic acid after the subject

10. Fletcher, W. M., and Hopkins, F. G.: Lactic Acid in Amphibian Muscle, J. Physiol. **35**:247, 1906-1907.

11. Meyerhof, O.: Zur Verbrennung der Milchsäure in der Erholungsperiode des Muskels, Arch. f. d. ges. Physiol. **175**:88, 1919.

had walked at a rate of 3½ miles (5.6 kilometers) per hour for twenty-eight minutes rose from 20.9 to 36.6 mg. Walking at the rate of 4⅒ miles (6.6 kilometers) per hour for thirty-three minutes induced a change of from 21.4 to 58.9 mg. In a later study Long [12] observed similar changes. Owles,[13] on the other hand, failed to observe changes in the blood from the veins of the arm in two trained subjects following a walk of thirty minutes at 4½ miles (7.2 kilometers) per hour. More recently, Cook and Hurst [14] investigated the lactic acid in man during rest and during exercise. In two subjects accustomed to walking long distances they observed no change in the lactic acid content of the blood following walking at 4 miles (6.4 kilometers) and at 4½ miles, respectively, per hour for thirty minutes. In two other subjects not accustomed to strenuous walking, a somewhat shorter walk was followed by a doubling of the blood lactic acid in the arm and femoral vein. In contrast to our experience, however, the rises in the femoral blood and in that of the arm were practically identical. The explanation of this apparent discrepancy may be the difference in the duration of the exercise; that is, following the longer exercise a complete mixing of the lactic acid throughout the blood occurred, so that the contents were in equilibrium. Cook and Hurst also emphasized that the threshold of exercise beyond which an increase of lactic acid appears in the blood depends on the fitness or training of the individual. There is little doubt that the discrepancies in the various findings are due partly to differences in methods of approach to the problem as well as to the delicacy of the method of lactic acid determination.

Eppinger, Kisch and Schwarz [2] presented evidence indicating that the resynthesis of lactic acid is one of the first disturbances in heart failure. The increased circulation of lactic acid in the blood is supposed to cause acidosis, which decreases the buffering capacity of the blood. These chemical alterations then place an increased burden on the heart, leading to failure. Eppinger and his associates did not study directly the utilization of oxygen by the working muscles or the overflow of lactic acid into the blood. Their method of approach was indirect, through a study of the respiratory function of the entire body. A few observations by Diaz and Cuenca [15] on the lactic acid content of the venous

12. Long, C. N. H.: Muscular Exercise, Lactic Acid, and the Supply and Utilisation of Oxygen: XIV. The Relation in Man Between the Oxygen Intake During Exercise and the Lactic Acid Content of the Muscles, Proc. Roy. Soc., London, s.B **99**:167, 1925-1926.

13. Owles, W. H.: Alterations in the Lactic Acid Content of the Blood as a Result of Light Exercise, and Associated Changes in the CO_2-Combining Power of the Blood and in the Alveolar CO_2 Pressure, J. Physiol. **69**:214, 1930.

14. Cook, L. C., and Hurst, R. H.: Blood Lactic Acid in Man During Rest, J. Physiol. **79**:443, 1933.

15. Diaz, C. J., and Cuenca, B. S.: Etudes cliniques sur l'utilisation de l'acide lactique, Ann. de méd. **28**:501, 1930.

blood at rest and following exercise may be looked on as a confirmation of Eppinger's contention. Hefter and Okunew[16] claimed that in the presence of rheumatic fever with cardiac decompensation and in a state of decompensation, regardless of its etiology, there is a decreased capacity of the muscles to utilize oxygen, and that the resynthesis of the lactic acid is disturbed.

In normal subjects we found that the oxygen utilization in the arm and that in the leg were approximately the same. When the patient stood for two minutes there was a considerably greater peripheral utilization both in the arm and in the leg, particularly in the leg. This increased utilization cannot be explained by an equivalent increase in the metabolism with an unchanged blood flow, for it was also present in the passive arm, which had an essentially unaltered metabolism. The change reflects a decreased blood flow through the extremities during standing, as was suggested by Florkin, Edwards and Dill.[17]

Immediately following exercise the average oxygen utilization more than doubled and then promptly (within ten minutes) returned to normal. The increased utilization of oxygen in the leg was undoubtedly due to the fact that the increased metabolism of the working muscles caused a demand for oxygen which was relatively greater than the increase in the blood flow to these muscles. It was particularly surprising, however, to find that the oxygen utilization in the resting arm had increased to practically the same degree as that in the exercising leg. This markedly increased oxygen utilization of the arm may be explained by a passively decreased blood supply to the arm, as a result of an increased blood flow in the leg, or by a local vascular constriction in the arm which retarded the blood flow. Such local reflex retardation of the blood flow in the resting tissues, when other tissues are active, has recently been demonstrated in animals by Rein.[18] It is this reflex regulation of the circulation which enables the working tissues to obtain a better blood supply. According to Bainbridge,[19] the oxygen supply to muscles during strenuous exercise may increase from ten to fifteen times. That the cardiac output cannot increase correspondingly is obvious, for it would necessitate an output of from 40 to 60 liters per minute, which with a heart rate of from 120 to 140 would yield a stroke volume of from 300 to 400 cc.—a physical impossibility. The regional constriction of the vascular areas during rest, however, not only results

16. Hefter, A. J., and Okunew, D. F.: Ueber Veränderungen des peripheren Stoffwechsels im Zusammenhang mit den Blutkreislaufstörungen bei der Muskelarbeit, Ztschr. f. d. ges. exper. Med. **79**:806, 1931.

17. Florkin, M.; Edwards, H. T., and Dill, D. B.: Oxygen Utilization in the Legs of Normal Men: I. Effect of Posture, Am. J. Physiol. **94**:459, 1930.

18. Rein, H.: Vasomotorische Regulationen, Ergebn. d. Physiol. **32**:28, 1931.

19. Bainbridge, F. A.: The Physiology of Muscular Exercise, ed. 3, New York, Longmans, Green & Co., 1931.

in a decreased flow of blood through these areas during rest but may be a factor in the elevation of the arterial blood pressure observed during exercise. The elevated arterial pressure makes the increased shunting of blood into the dilated vascular regions of the working areas particularly effective, because it makes possible a considerably increased regional blood flow without an increase in cardiac work.

The increase in the lactic acid in the femoral venous blood after exercise was, of course, due to the fact that the acid was formed in the active muscle faster than it could be either resynthesized in situ or conveyed away by the blood stream to undergo reconversion into glycogen or oxidation in the liver or elsewhere.

It is significant that the immediate change in the lactic acid of the blood of the arm was slight. Ten minutes later, however, the level was similar in the arm and in the leg. These observations definitely indicate that moderate muscular exercise which is carried out by the subjects with ease is followed by a considerable output of lactic acid into the blood. As a result of the mixing effect, an equalization of the lactic acid level throughout the circulation occurs within ten minutes.

In patients with heart disease and with moderate impairment of cardiac reserve, but with no evidence of failure, who with two exceptions performed the exercise without dyspnea the behavior of the peripheral circulation was similar to that in the control group. The only striking difference was the higher basal heart rate, with a greater increase and a slower return to the level present during rest. The same work was performed, therefore, with a greater expenditure of cardiac energy.

The group with obvious evidence of failure of the circulation without peripheral engorgement included patients with cardiac lesions of varied etiology. The degree of functional impairment varied from moderate to severe, but in no case was it so severe as in the group with congestive failure. The venous pressures were within normal limits, but the vital capacity was appreciably reduced. This group also showed essentially the same oxygen utilization and lactic acid level during rest as did the control group; following exercise, however, there were a somewhat greater peripheral utilization of oxygen and a somewhat greater output of lactic acid. The differences statistically are not conclusive. Patients in this group also exhibited a marked rise and a slow return of the heart rate following exercise. It was significant that several patients who were barely able to perform the moderate exercise because of intense dyspnea showed normal oxygen utilization and lactic acid output. This group of patients clearly demonstrates that the source of disability does not lie in the inadequacy of the peripheral circulation. We have presented elsewhere [8b] evidence of disturbance of the pulmonary circuit in this type of patient.

The patients with congestive failure were completely disabled. The vital capacities of the lungs were conspicuously low; the venous pressures,

rather high. Their peripheral oxygen utilization was higher than normal, both during rest and following exercise. The lactic acid outputs were also greater than in the control group. It is particularly significant that the average level of the lactic acid during rest was essentially the same as in the control group. Our results, therefore, do not indicate a relationship between the degree of circulatory insufficiency and the level of the lactic acid during rest. As some of the patients showed a high oxygen utilization and a slow blood flow, it follows that the lactic acid during rest may not be appreciably influenced by a slow blood flow. The same lack of correlation between the degree of blood flow and the level of lactic acid in individual cases was observed after exercise.

The finding of high oxygen utilization at rest indicates a decreased cardiac output in these patients. Moreover, the fact that this utilization increased after exercise to such an extent that there was in several

TABLE 4.—*The Lactic Acid During Rest in Eleven Patients with Hepatic Disease*

Patient	Lactic Acid During Rest, Mg. per 100 Cc.	Diagnosis
G. O'M.	11	Catarrhal jaundice
W. A.	15	Catarrhal jaundice
W. C.	13	Arsphenamine hepatitis
H. M.	18	Arsphenamine hepatitis
S. K.	25	Jaundice? carcinoma of the liver
M. L.	14	Cirrhosis of the liver
W. B.	16	Cirrhosis of the liver
T. R.	18	Cirrhosis of the liver; arteriosclerotic heart disease
R. K.	21	Cirrhosis and acute hepatitis
J. L.	27	Toxic hepatitis
M. G.	18	Acute yellow atrophy

instances an unusually low oxygen content of the femoral venous blood suggests that the rise in output after exercise was insufficient and frequently inadequately compensated by the increase in the peripheral utilization of oxygen.

Our experience, therefore, does not agree entirely with the observations of Meakins and Long,[20] who observed, even during rest, an increased concentration of the blood lactic acid in patients with severe circulatory failure and who considered that the amount of lactic acid in the blood is in proportion to the severity of the circulatory failure. There is a possibility, however, that in patients with cardiac disease who are moribund or who have severe hepatic damage the lactic acid level is elevated, but we have not studied this aspect of the problem. In some patients with normal cardiovascular systems and with hepatic damage alone we have observed an elevated lactic acid content of the blood (table 4). Although the lactic acid level of the blood in patients with cirrhosis of the liver may be high, the response to exercise of two subjects was of essentially the same character as in normal subjects.

20. Meakins, J., and Long, C. N. H.: Oxygen Consumption, Oxygen Debt and Lactic Acid in Circulatory Failure, J. Clin. Investigation **4**:273, 1927.

COMMENT

As a result of these studies, therefore, we consider that there is no evidence of a primary disturbance of the peripheral circulation as the precipitating factor in heart failure. There is evidence, however, that the peripheral circulation does not play a purely passive rôle, as was once widely believed. In normal persons, the cardiovascular functions can be increased efficiently and a certain amount of the load removed from the heart itself by peripheral vascular reflexes which tend to shunt blood where it is most needed and under greater pressure, particularly by increased oxygen utilization. The same factors, to a greater degree, tend to operate in patients with heart disease, with and without evidence of failure. With the aid of the peripheral circulation, compensation for an inadequate cardiac function may be achieved. Indeed, failure of the peripheral circulation as measured by an inadequate supply of oxygen to the tissues is usually a late manifestation of what is commonly thought of as "congestive heart failure." Frequently it never occurs, for long before it becomes a significant factor in the clinical picture, gross disturbances of the pulmonary circulation as a result of the failing heart incapacitate the patient or lead to his death.

SUMMARY AND CONCLUSIONS

1. The utilization of oxygen and the production of lactic acid in the upper and lower extremities were compared in normal subjects and in patients having heart disease with and without congestive failure.

2. During rest, the average oxygen utilization was essentially the same in the arm and in the leg. In heart disease without congestive failure the utilization of oxygen during rest was normal in magnitude, but with congestive failure there was a tendency toward an increased peripheral utilization. This is evidence that in congestive failure the blood flow through the extremities is frequently reduced. Edema of the leg was not found to be associated with a relatively or absolutely increased local blood flow.

3. On standing, the oxygen utilization of the extremities increased both in subjects with normal and in those with diseased cardiovascular systems, as a result, in part, at least, of decreased blood flow.

4. Immediately after exercise the oxygen utilization increased markedly, but it returned to the level during rest within ten minutes. In a patient with heart disease the oxygen content of the femoral venous blood immediately after exercise was as low as 1.1 volumes per cent.

5. The average resting level of the lactic acid in the extremities was between 12 and 14 mg. for all groups. Immediately after the patients ceased walking, the lactic acid of the femoral venous blood draining the active muscle more than doubled; it then fell rapidly during the next

ten minutes but did not reach the level observed during rest within twenty minutes. The lactic acid content of the venous blood of the inactive arm rose slightly immediately after the exercise, but in ten minutes was similar to that of the leg, as a result of the mixing effect of the circulation. With the increasing severity of circulatory failure there was a tendency for the femoral lactic acid to rise to a higher level than normal immediately after exercise and to fall more slowly.

6. With the exception of one case of congenital intraventricular septal defect, the etiology of the heart disease played no rôle in the nature of the peripheral circulatory response.

7. Certain patients showed marked cardiac disability, i. e., orthopnea, dyspnea and low vital capacity of the lungs, and yet they had normal venous pressure, no edema or hepatic enlargement and normal oxygen utilization and lactic acid response. The disability in these patients cannot be explained on the basis of the behavior of the peripheral circulation. When disturbances in the lactic acid production and peripheral circulation occur, they are the result, and not the cause, of heart failure.

This investigation was conducted with the technical assistance of Miss Dwight Baker and Miss Rose Shore.

Progress in Internal Medicine

LIVER AND BILIARY TRACT

REVIEW OF THE LITERATURE OF 1933 AND 1934

CARL H. GREENE, M.D.
Associate in Medicine and Associate Attending Physician

Z. BERCOVITZ, M.D.
Instructor in Medicine and Junior Assistant Physician

AND

EILIF C. HANSSEN, M.D.
Instructor in Surgery and Junior Assistant Surgeon

NEW YORK

Mann,[1] in a review entitled "The Functions of the Gall Bladder," published in 1924 a bibliography of 95 articles. Ivy,[2] in a similar review in 1934, published a bibliography of 553 articles, the majority of which represented work done during the intervening decade. The contrast between these two reviews illustrates dramatically both the widespread interest in this field of medicine and the voluminous nature of the resultant literature. This is true not only of the physiology of the gallbladder but of that of the liver and the rest of the biliary tract. Under these conditions it seemed best in reviewing the literature for 1933 and 1934 to outline, so far as possible, the more important trends of investigation by citing significant papers rather than to attempt reference to the entire literature for these years.

PHYSIOLOGY OF THE GALLBLADDER

Ivy,[2] in reviewing the physiology of the gallbladder, pointed out that during the past decade no really new activities or functions have been discovered which had not been suggested before but that it is now believed that the physiology of the gallbladder resembles in principle the general activities of the intestine, namely, absorption, secretion and motor activity.[3]

From the Departments of Medicine and Surgery, New York Post-Graduate Medical School and Hospital.

1. Mann, F. C.: The Functions of the Gall Bladder, Physiol. Rev. **4**:251 (April) 1924.

2. Ivy, A. C.: The Physiology of the Gall Bladder, Physiol. Rev. **14**:1 (Jan.) 1934.

3. Harding, H. E.: Functions of the Epithelium of the Gallbladder, Guy's Hosp. Rep. **84**:186 (April) 1934.

The gallbladder is one of the mechanisms concerned in the correlation of the secretory activity of the liver and the digestive activity of the other portions of the gastro-intestinal tract. According to the classic concept, this viscus stores and concentrates much of the bile secreted by the liver during the interdigestive period in order to supply this store of concentrated bile at the beginning of the next digestive period and so to aid in the digestion and absorption of fatty foods in particular. This functional activity is made possible by the coordinated action of the three types of primary activity to which reference has been made.

The normal gallbladder concentrates the hepatic bile that enters it to a density from four to ten times that of the original. This is accomplished primarily by the absorption of water and inorganic salts so that the bile tends to come into osmotic equilibrium with the blood serum. In this process of concentration the bile is slightly acidified. The other biliary constituents appear to be absorbed only slightly, if at all, by the normal gallbladder, though there are many questions with regard to details which remain to be decided.

It is probable that under normal conditions the gallbladder proper forms only a small quantity of mucoid secretion. In conditions of acute irritation it ceases to concentrate hepatic bile and instead pours out a fluid which may vary widely from the normal bile in its composition. Because of the change in the concentrating power of the gallbladder the composition of the bile, as emphasized by Ravdin and his associates,[4] may show great variations in disease.

The gallbladder manifests two types of motor activity. One type may be called a tonic contraction. It produces a sustained rise in pressure which persists from five to thirty minutes or more. The other type may be called a tonus rhythm and is manifested by rhythmic contraction and relaxation occurring at a rate of from 2 to 6 times a minute. In each type the muscular coat may contract either as a whole or in part. In some species there may be a peristalsis-like type of motor activity during evacuation.

While formerly there was controversy as to whether the gallbladder ever emptied, this can now be accepted as a fact. Once it is agreed that the gallbladder does become evacuated, consideration of the mechanism involved becomes paramount. The usually accepted view is that evacuation is the result of muscular contraction, though some investigators, as Marrazzi,[5] still deny such activity. Ivy[6] and his students

4. Ravdin, I. S.; Riegel, C.; Johnston, C. G., and Morrison, P. J.: Studies in Biliary Tract Disease, J. A. M. A. **103**:1504 (Nov. 17) 1934.

5. Marrazzi, A. S.: Emptying of Gallbladder, Am. J. Physiol. **102**:293 (Nov.) 1932.

6. Ivy, A. C.: Factors Concerned in the Evacuation of the Gall Bladder, Medicine **11**:345 (Sept.) 1932.

demonstrated that the presence of acid or of fatty substances in the duodenum and upper portion of the intestine causes the formation of a hormone (cholecystokinin) which stimulates contraction of the gallbladder. Ivy expressed the belief that the contraction and evacuation of the gallbladder are due primarily to the stimulus of this hormone.

The efficiency of such fatty substances as cream, egg yolk, olive oil and oleic acid in producing contraction and emptying of the gallbladder is to be explained rather by their action in stimulating the production of cholecystokinin in the mucosa of the duodenum than by a specific stimulatory effect of these materials either on nerve endings in the duodenum before, or on the wall of the gallbladder after, absorption. Ivy also showed the effectiveness of cholecystokinin in causing emptying of the gallbladder in man.

The importance of the sphincteric mechanism at the duodenal end of the common duct, as pointed out by Giordano and Mann,[7] must not be minimized. Ivy, Voegtlin and Greengard [8] recently reported experiments on a human subject in whom, after the injection of a solution of cholecystokinin, pain in the gallbladder was produced by the contraction of the gallbladder concurrently with the development of spastic obstruction in the intramural portion of the common bile duct. In this case intraduodenal administration of magnesium sulphate was effective in relieving the spasm and distress. Since cholecystokinin is formed after the eating of fats, functional disturbances analogous to those reported by Ivy, Voegtlin and Greengard may explain some of the intolerance of fats which is a frequent complaint of patients with chronic cholecystitis. In addition to this humoral mechanism, the gallbladder is under the control of the nervous system and possesses sensory and motor innervation. The efferent fibers from the vagus nerve are predominantly motor in character; those from the splanchnic nerves, inhibitory. The motor activity of the duodenal musculature and the sphincter of Oddi likewise are subject to nervous regulation, and the view of a reciprocal relationship between the emptying of the gallbladder and the relaxation of the sphincter is generally accepted though many of the details regarding the exact mechanism involved are still unexplained.

Ivy described the evacuation of the gallbladder after a meal of egg yolk and cream as due primarily to a more or less sustained tonic contracture of the musculature. The contraction is excited in part by a

7. Giordano, A. S., and Mann, F. C.: The Sphincter of the Choledochus, Arch. Path. **4**:943 (Dec.) 1927.

8. Ivy, A. C.; Voegtlin, W. L., and Greengard, H.: The Physiology of the Common Bile Duct: A Singular Observation, J. A. M. A. **100**:1319 (April 29) 1933.

hormone (cholecystokinin) and in part by a reflex nervous mechanism. The sphincter of Oddi and the duodenal musculature relax and permit bile to be expelled by the contracting gallbladder. Duodenal peristalsis may exert a milking action on the intramural portion of the common duct which assists but is not essential to evacuation. Following evacuation which may be but usually is not complete, the common duct is closed by the choledochoduodenal barrier, and the gallbladder relaxes as hepatic bile again enters the reservoir.

When one considers the several mechanisms and the precise integration of their action which is necessary for the normal functioning of the gallbladder and biliary tract and the variety of influences which may affect one or the other of the mechanisms, the existence of functional disorders of motility, the so-called biliary dyskinesia, is not surprising. An extensive literature on this topic has developed in Germany during the past decade which Ivy and Sandblom [9] have recently reviewed. Biliary dyskinesia is an important clinical problem, and its solution will serve to explain many otherwise obscure clinical observations. It deserves much more widespread clinical recognition and study than it receives at the present time. For instance, it is a common observation during duodenal drainage to find that no concentrated bile is obtained after stimulation with magnesium sulphate but that a free flow follows the instillation of egg yolk or olive oil. Does such an observation indicate that in that patient reflex stimulation was insufficient to cause evacuation of the gallbladder, which did, however, respond to hormonal stimulation? Can this method be used to study the relative influence of the two mechanisms in an individual patient?

DIAGNOSIS AND TREATMENT OF CHRONIC CHOLECYSTITIS

Numerous authors, among them Twiss and Greene [10]; Lyon [11]; Dreier, Crellin and Rehfuss [12]; Brown,[13] and Ivy and Bergh [14] presented brief reviews of the physiology of the gallbladder and pointed

9. Ivy, A. C., and Sandblom, P.: Biliary Dyskinesia, Ann. Int. Med. **8**:115 (Aug.) 1934.

10. Twiss, J. R., and Greene, C. H.: Dietary and Medical Management of Diseases of the Gall Bladder: Newer Points of View, J. A. M. A. **101**:1841 (Dec. 9) 1933.

11. Lyon, B. B. V.: Diagnosis and Management of Gall Tract, Particularly Gall Bladder Disease, Am. J. Digest. Dis. & Nutrition **1**:18 (March) 1934.

12. Dreier, J. F.; Crellin, W. N., and Rehfuss, M. E.: The Physiology of the Gall Bladder, Rev. Gastroenterol. **1**:24 (March) 1934.

13. Brown, T. R.: The Results of Treatment—Medical and Surgical—in Gall Bladder Disease from a Clinician's Viewpoint, Am. J. Digest. Dis. & Nutrition **1**:221 (June) 1934.

14. Ivy, A. C., and Bergh, G. S.: The Applied Physiology of the Extra Hepatic Biliary Tract, J. A. M. A. **103**:1500 (Nov. 17) 1934.

out the application of the newer points of view to improvement of the diagnosis and therapeutic management of the patient with disease of the liver or biliary tract. They emphasized that the three most important elements in the diagnosis of cholecystic disease are (1) the history of the case, (2) cholecystography and (3) nonsurgical drainage of the biliary tract.

The history remains of paramount importance in diagnosis. Brown in particular emphasized the value of a carefully taken, thorough and well studied history, comprising not only the record of the digestion but the entire history of the patient. By this means and a careful physical examination, he was able to make the correct diagnosis in slightly less than 85 per cent of the cases which he reported.

Cholecystography.—The value of the cholecystogram in the diagnosis of disease of the gallbladder is universally accepted. An attempt to evaluate the reliability of the method by statistical analysis is difficult because of the various factors which enter into the selection of the patients on whom this procedure is performed. Ferguson and Palmer,[15] who reported a study of 2,070 cases, concluded that good visualization of the gallbladder and no evidence of stones indicated the diagnosis of a normal gallbladder with an accuracy of probably over 98 per cent. The accuracy of diagnosis when stones were visualized, either as positive or negative shadows, likewise approached 100 per cent. When visualization of the gallbladder failed and there was a clinical history of cholecystitis, the diagnosis was later proved to be correct in 90 per cent of the cases. If the clinical history was lacking, the diagnostic accuracy was less than 66.6 per cent. The authors found that in the cases in which cholecystic disease was demonstrated at operation a history of colic was noted almost as frequently as cholecystographic evidence of the lesion. Ferguson and Palmer used the intravenous method of administering the dye. Buisson[16] and Hess[17] likewise stressed the value of the intravenous method in obtaining the cholecystogram.

Kirklin[18] pointed out that when the oral method is properly executed its efficiency is equal to that of the intravenous method. In a series of 732 cases in which the diagnosis was established at operation, he

15. Ferguson, A. N., and Palmer, W. L.: Cholecystography: Its Clinical Evaluation: A Study of Two Thousand and Seventy Cases, J. A. M. A. **100**:809 (March 8) 1933.

16. Buisson, P.: Interpretation of Negative Cholecystogram, Presse méd. **41**: 1386 (Sept. 6) 1933.

17. Hess, L. R.: X-ray in Diagnosis of Gallbladder Disease, Canad. M. A. J. **29**:396 (Oct.) 1933.

18. Kirklin, B. R.: Persisting Errors in the Technic of Oral Cholecystography: A Procedure Designed to Avoid Them, J. A. M. A. **101**:2103 (Dec. 30) 1933.

found the accuracy of the cholecystogram in revealing a normal gallbladder was 89.5 per cent. Gallstones were detected in 70.8 per cent of the cases, but evidence of cholecystic disease was present in 99 per cent. Of the patients showing changes in the cholecystogram, 98.6 per cent had cholecystic disease. Foged [19] also reported similar results with the oral administration of the contrast substance.

The feeding of carbohydrate results in the secretion of concentrated bile by the liver and at the same time favors storage of that bile in the gallbladder. Antonucci,[20] in particular, pointed out that the intravenous injection of 125 cc. of a 40 per cent solution of dextrose followed by the intravenous injection of 3 Gm. of tetiothalein sodium produced rapid elimination of the dye and distention of the gallbladder so that maximum opacity of the dye in the gallbladder was obtained in two hours. Liverani,[21] Zappala [22] and others confirmed the advantages of this technic. Stewart and Illick [23] used the same principle in improving the technic of cholecystography by the oral method. The patient is given several cups of tea with extra sugar in the afternoon. The regular evening meal is allowed at 6 p. m., and the first dose of tetiothalein sodium is given at 7 p. m. Tea with sugar is given later in the evening. The following morning no breakfast is allowed, and cholecystograms are taken twelve and sixteen hours after the first dose of the dye. The noon meal consists of fruit juice, jello, fruit salad and tea, and it is followed by another dose of the dye. Tea is again given in the afternoon, and an evening meal similar to the luncheon is allowed. A third dose of dye is given in the evening. A thirty-six hour examination is made the next morning. The films normally exhibit marked concentration of opaque bile in the gallbladder. A study is then made after a fatty meal to determine how well and rapidly the gallbladder empties. When carried out successfully, such methods promise to increase even further the precision of the cholecystographic methods of diagnosis.

Nonsurgical Drainage of the Biliary Tract.—The diagnostic value of nonsurgical drainage of the biliary tract is a matter concerning which there is the widest divergence of opinion. When the new type

19. Foged, J.: Cholecystography, Acta chir. Scandinav. **75**:1105 (June 8) 1934.

20. Antonucci, C.: Rapid Cholecystography, Presse méd. **40**:983 (June 22) 1932.

21. Liverani, E.: Biochemical and Experimental Research in Rapid Cholecystography of Antonucci and Modification of Method, Policlinico (sez. med.) **40**:128 (Feb.) 1933.

22. Zappala, G.: Cholecystography According to Antonucci's Method, Policlinico (sez. chir.) **40**:541 (Sept. 15) 1933.

23. Stewart, W. H., and Illick, H. E.: Intensified Oral Cholecystography: Preliminary Report, Am. J. Digest. Dis. & Nutrition **1**:337 (July) 1934.

of tip with a terminal weight and the simplified technic described by Twiss [24] are used, it is not a formidable procedure and can be used as a routine to aid in the diagnosis. In our experience [25] the presence or absence of concentrated bile, especially if this can be confirmed by chemical methods, and the conditions under which the concentrated bile is obtained give evidence regarding both the concentrating power and the motor activity of the gallbladder. As such, the findings afford a valuable confirmation of those obtained by cholecystography. The finding of crystals of cholesterol or of calcium bilirubinate in quantity, as Rousselot and Bauman [26] agreed, is strong presumptive evidence of the presence of biliary calculi.

Cultures obtained from the bile and the demonstration of the presence of Bacillus typhosus, as pointed out by Bigelow and Anderson [27] and by Senftner and Coughlin,[28] are essential in the recognition of typhoid carriers, especially if cholecystectomy is to be done for the cure of the carrier state.

Treatment.—The factors of stasis, metabolic disturbance and infection are generally accepted as of prime importance in the production of cholecystitis or cholelithiasis. While the clinician may make a diagnosis of cholecystitis, it is now generally accepted that the pathologic process is not limited to the gallbladder but that the entire biliary tract is affected to a greater or less extent. The problem of the physician is not the cure of an acute condition but the management of a chronic disease. Treatment is aimed at the relief or correction of the elements of stasis, metabolic disturbance and infection. As already pointed out, these conditions may result from a variety of causes, and the details of the method of treatment may vary with the individual patient. Under these conditions surgical drainage or removal is but one factor, though often a major one, in the management of disease of the biliary tract. Surgical intervention is indicated in the presence of

24. Twiss, J. R.: A New Type of Duodenal Tube Tip, Am. J. M. Sc. **185**:109 (Jan.) 1933; Technic of Nonsurgical Drainage of the Biliary Tract, J. A. M. A. **100**:792 (March 18) 1933.

25. Carter, R. F.; Greene, C. H., and Twiss, J. R.: Diagnosis and Treatment of Diseases of the Liver and Biliary Tract, New York, New York Post-Graduate Medical School, 1934.

26. Rousselot, L. M., and Bauman, L.: Cholesterol Crystals and "Calcium Bilirubinate Granules": Their Significance in Bile Obtained Through the Duodenal Tube, J. A. M. A. **100**:254 (Jan. 28) 1933.

27. Bigelow, G. H., and Anderson, G. W.: Cure of Typhoid Carriers, J. A. M. A. **101**:348 (July 29) 1933.

28. Senftner, H. F., and Coughlin, F. E.: Typhoid Carriers in New York State with Special Reference to Gall Bladder Operations, Am. J. Hyg. **17**:711 (May) 1933.

gallstones and in a few cases with characteristic history and symptomatology. Graham and Mackey [29] pointed out that in the absence of severe pain or typical biliary colic the results of cholecystectomy in cases of stoneless gallbladder are likely to be unsatisfactory in approximately 40 per cent of the patients. Furthermore, they added that at present there seems to be little justification for operation in patients who have only the early beginnings of cholecystic disease, unless one is interested in the prevention of complications. Brown [13] and Howard,[30] in reporting a series of 84 cases observed for from two to fifteen years, stated that in only 59 per cent did the patient have complete or relative cure following operation.

The importance of careful follow-up in either medical or surgical cases is shown by the report of Blackford, King and Sherwood.[31] They studied 200 patients with chronic cholecystitis who had been treated medically for from five to fifteen years. Thirty-seven per cent of the patients had satisfactory relief for an average period of more than eight years without operation. Forty-eight per cent either came to operation later because of continuation of symptoms or should have been operated on for that reason. Fifteen per cent of the patients died, but in only 1 per cent was death due directly to disease of the gallbladder.

JAUNDICE

During the two years under consideration there has been no change in the views generally held regarding the pathogenesis of jaundice. Mann and Bollman,[32] who summarized much of the experimental investigation, pointed out that complete removal of the liver produces jaundice which may be considered as entirely hemolytic in origin. In this condition the bilirubin of the serum is increased and gives only the indirect reaction to the van den Bergh test. In other types of experimental jaundice produced by hepatic injury or by occlusion of the bile duct, the serum bilirubin is increased, and the van den Bergh reaction is direct. This observation affords complete agreement between the

29. Graham, E. A., and Mackey, W. A.: A Consideration of the Stoneless Gallbladder, J. A. M. A. **103**:1497 (Nov. 17) 1934.

30. Howard, J. T.: An Analysis of the Results of Biliary Tract Surgery, Am. J. Digest. Dis. & Nutrition **1**:270 (June) 1934.

31. Blackford, J. M.; King, R. L., and Sherwood, K. K.: Cholecystitis: Study Based on Follow-Up After from Five to Fifteen Years of Two Hundred Patients Not Operated On, J. A. M. A. **101**:910 (Sept. 16) 1933.

32. (*a*) Mann, F. C., and Bollman, J. L.: Jaundice: A Review of Some Experimental Investigations, J. A. M. A. **104**:371 (Feb. 2) 1935. (*b*) Bollman, J. L., and Mann, F. C.: Liver and Bile, Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1934, vol. 3, p. 367.

experimental and the clinical types of hemolytic, hepatic and obstructive jaundice.

Bollman and Mann [32b] further pointed out that in experimental obstructive jaundice the absence or alteration of bile from the intestine, the presence of biliary constituents in the blood and tissues and the associated functional impairment of the liver produce typical effects on the experimental animal. Nutritional disturbances and especially the decreased tolerance to meat are important. There is a tendency to the development of peptic ulcer. Anemia and a decrease in the proteins of the blood plasma are frequent, and ascites may be found. A reduction in the formation of bile salts is also a result of hepatic injury.

The clinical classification of jaundice requires no discussion at the present time. However, reference may be made to the studies of Snelling,[33] Altzitzoglou [34] and Fuchs [35] on icterus neonatorum. They pointed out, as have other investigators, that during fetal life the liver is actively concerned in the formation of red blood cells and polycythemia is present. During the first two weeks of life the red cell count and the percentage of hemoglobin fall gradually. Excretion of bilirubin by the fetal liver is at a minimum, and during the first few days after birth there is a period of hepatic insufficiency until the excretion of bilirubin attains its normal degree of activity. The usual type of icterus neonatorum develops during this period. In addition to this benign type of icterus neonatorum, cases of icterus gravis are also seen in new-born infants. The majority of these cases are due either to infection or, in the familial type, to erythroblastosis.

The pathogenesis of "catarrhal" jaundice continues to be a source of controversy. It is accepted that while the majority of the cases of this condition are due to toxic or degenerative changes in the hepatic parenchyma, some may be due to infection of the smaller bile ducts or to capillary cholangeitis, and in a few cases there may be true gastroduodenal catarrh with obstruction of the common bile duct by a mucous plug. Hurst and Simpson [36] reviewed the literature dealing with the pathogenesis of this condition; they insisted that the various syndromes can be recognized clinically. In true catarrhal jaundice the cases occur sporadically in young persons. Jaundice is preceded by a period of anorexia, malaise, fever, nausea and gastro-intestinal disturbances. The liver is slightly enlarged and tender, and the gallbladder can frequently

33. Snelling, C. E.: Icterus Neonatorum, J. Pediat. **2**:399 (April) 1933.

34. Altzitzoglou, J.: Blood Picture in Icterus Neonatorum Familaris Gravis and Its Diagnostic Significance, Monatschr. f. Kinderh. **58**:329, 1933.

35. Fuchs, H.: Icterus Neonatorum Gravis with Especial Consideration of Infectious Type, Schweiz. med. Wchnschr. **63**:1129 (Nov. 4) 1933.

36. Hurst, A. F., and Simpson, C. K.: Catarrhal Jaundice and Mild Hepatic Necrosis: Their Pathology and Diagnosis, Guy's Hosp. Rep. **84**:173, 1934.

be palpated. The levulose or galactose test of hepatic function gives negative results. In cases of primary parenchymal injury or necrosis, on the other hand, there may be a history of exposure to a toxic substance, such as arsphenamine or cinchophen, but otherwise the jaundice develops without prodromal symptoms. Following the appearance of jaundice, there develop anorexia, headache, weakness and tachycardia. This conception of Hurst is one of extreme interest. However, there are many cases of acute hepatic jaundice in which the clinical findings do not permit so distinct a differential diagnosis.

In many cases of jaundice, as pointed out by Flood, Seegal, Spock and Loeb,[37] even the differentiation of a hepatic from an obstructive type of icterus is difficult. It is in these cases in particular that the tests of hepatic function have been of greatest usefulness.

TESTS OF HEPATIC FUNCTION

Carbohydrate Metabolism.—The rôle of the liver in carbohydrate metabolism is accepted, but the selection of the proper test to demonstrate changes in this activity of the liver is a cause of controversy. Althausen, Gunther, Lagen and Kerr [38] gave 20 units of insulin to a fasting patient; twenty minutes later 50 Gm. of dextrose in 500 cc. of water was administered orally, followed by a liter of water. By this means they thought they could obtain the simultaneous measurement of the glycogen reserve, the dextrose metabolism and the water-regulating function of the liver. Migneco [39] and Ricketts [40] tried this test on normal persons and on patients with hepatic disease. They found no essential difference between the behavior of the group of normal persons and that of patients with hepatic disease, and they did not consider the test a satisfactory measure of hepatic function.

The various factors which influence the tolerance to levulose were discussed in detail by Rowe, Plummer and McManus.[41] They empha-

37. Flood, C. A.; Seegal, D.; Spock, B., and Loeb, R. F.: Differential Diagnosis of Jaundice: Study of Two Hundred and Thirty-Five Cases of Nonhemolytic Jaundice Due to Carcinoma, Calculus in Common Bile Duct and Liver Degeneration, Am. J. M. Sc. **185**:358 (March) 1933.

38. Althausen, T. L.; Gunther, L.; Lagen, J. B., and Kerr, W. J.: Modification of the Dextrose Tolerance Test as an Index of the Metabolic Activity of the Liver, Arch. Int. Med. **46**:482 (Sept.) 1930.

39. Migneco, G.: Practical Value of New Test of Hepatic Function, Policlinico (sez. prat.) **40**:845 (May 29) 1933.

40. Ricketts, H. T.: Function of Liver: Appraisal of Modified Dextrose Tolerance Test, Arch. Int. Med. **52**:147 (July) 1933.

41. Rowe, A. W.; Plummer, A. J., and McManus, M. A.: The Metabolism of Levulose: I. Some Considerations on Provocative Levulosuria, Am. J. M. Sc. **186**:15 (July) 1933.

sized the variability of the tolerance even in normal persons, the difficulties in the use of changes in the amount of blood sugar to indicate divergences from the normal tolerance and the various physiologic factors, especially those of endocrine origin, which affect the use of tolerance to levulose as a test for hepatic disturbances.

The levulose tolerance test, nevertheless, has its proponents; the most recent one is Kimball,[42] who reported on 430 patients. Three hundred and thirty of the patients had some degree of hepatic insufficiency, and 45 per cent of this group gave a positive reaction. Rao [43] likewise found that the levulose tolerance test gave positive results in a greater number of patients with disease of the liver than in those without evidence of hepatic disorder. Positive results were most frequent in cases in which there had been acute destruction of the hepatic parenchyma. In cases of cirrhosis, the results were more variable, presumably owing to the variable extent to which hepatic tissue had been regenerated. A negative reaction, therefore, does not exclude hepatic disease. Rao preferred levulose to galactose for the testing of hepatic function.

Galactose at the present time is the most popular sugar for use in the test for hepatic function. Zadek and his co-workers,[44] Banks, Sprague and Snell,[45] Tumen and Piersol,[46] Rosenberg,[47] Singer and Wechsler [48] and Schiff and Senior [49] reported on the study of this test in various types of hepatic disease with particular reference to the differential diagnosis of jaundice. All of these authors were agreed that a positive reaction, that is, a urinary excretion of more than 3 Gm., is indicative of diffuse parenchymal injury to the liver, but the results

42. Kimball, S.: The Levulose Tolerance Test: A Study of Its Value with Especial Reference to Mild and Chronic Disease of the Liver, Guy's Hosp. Rep. **82**:157 (April) 1932.

43. Rao, M. V. R.: Investigation into Clinical Values of Levulose and Galactose Tolerance Tests for Hepatic Function, Indian J. M. Research **21**:141 (July) 1933.

44. Zadek, E.; Tietze, A., and Gebert, K.: Evaluation of Functional Tests of Liver at Bedside, Klin. Wchnschr. **12**:60 (Jan. 14) 1933.

45. Banks, B. M.; Sprague, P. H., and Snell, A. M.: Clinical Evaluation of the Galactose Tolerance Test, J. A. M. A. **100**:1987 (June 24) 1933.

46. Tumen, H. J., and Piersol, G. M.: Value of Alimentary Galactosuria in Diagnosis of Jaundice, Ann. Int. Med. **7**:311 (Sept.) 1933.

47. Rosenberg, D. H.: The Galactose and Urobilinogen Tests in the Differential Diagnosis of Obstructive and Intrahepatic Jaundice, Ann. Int. Med. **8**:60, 1934.

48. Singer, K., and Wechsler, L.: Clinical Significance and Pathogenic Mechanism of Agalactosuria, Wien. klin. Wchnschr. **47**:77 (Jan. 19) 1934.

49. Schiff, L., and Senior, F. A.: A Study of One Hundred Cases of Jaundice with Particular Reference to Galactose Tolerance, J. A. M. A. **103**:1924 (Dec. 22) 1934.

obtained in cases of the various types of disease were not uniform. Schiff and Senior, for example, obtained positive reactions in over 93 per cent of the cases of acute toxic or infectious hepatitis, while negative results were uniformly the rule in cases of obstructive jaundice. They, therefore, considered the test to be of great value in differentiating the two forms of jaundice. Zadek, on the other hand, reported positive results in only 50 per cent of the cases studied. Banks, Sprague and Snell obtained positive reactions in 83 per cent of their cases of acute hepatitis and in 38 per cent of those of obstructive jaundice. They, therefore, insisted that while the test is of value it is not pathognomonic and that the results must be weighed against the other clinical findings in the individual case.

Because of the possibility that variations in the rate of absorption of galactose from the intestine or in the excretion of galactose by the kidney will affect the results of the tolerance test as usually performed, Jankelson and Lerner [50] injected 25 Gm. of sugar intravenously and then observed the changes in the galactose content of the blood. Seven normal persons and 8 patients with hepatic disease were studied. In the normal subjects the galactose disappeared from the blood stream within an hour. Minimal degrees of hepatic damage were not shown, but in the presence of demonstrable damage the galactose was metabolized at a slower rate and retained in the blood. Positive results were obtained in all the cases of jaundice, though the changes were most marked in those of hepatitis. The series of cases reported, however, was too small to permit final conclusions regarding the diagnostic usefulness of this method of studying galactose tolerance.

Pavel, Florian and Radvan [51] also studied the galactose test in a series of cases of jaundice. They found that administration of insulin reduced the degree of galactosuria. In addition, they studied the lipolytic activity of the pancreatic juice and the diastatic activity of the urine as guides to the secretion of the pancreas. Changes which they interpreted as indicating pancreatic insufficiency were found in 15 of 17 cases of catarrhal jaundice. Similar changes, though less frequent, were found in cases of hepatic cirrhosis. Because the results of the galactose tolerance test paralleled the tests of pancreatic function, Pavel and his associates expressed the belief that the changes in galactose tolerance must be explained as due to pancreatic rather than to hepatic disturbances.

---

50. Jankelson, I. R., and Lerner, H. H.: Intravenous Galactose Liver Function Test: Preliminary Report, Am. J. Digest. Dis. & Nutrition **1**:310 (July) 1934.

51. Pavel, I.; Florian, I., and Radvan, I.: Significance of Testing for Carbohydrates, Especially Galactose, in Functional Examination of Liver, Ann. de méd. **35**:380 (May) 1934.

The possibility of pancreatic involvement in association with hepatic disease was also emphasized by Michelazzi,[52] who reported that the elevation of the blood sugar in a dextrose tolerance test is diminished if hydrochloric acid is given with the dextrose. He thought that the acid stimulates the production of pancreatic secretion and increases the production of both insulin and the external secretion of the pancreas. Foged [53] found a pathologic degree of diastasuria in patients with biliary calculi or cholecystitis. This was ascribed to infection or irritation of the pancreas secondary to inflammatory changes in the biliary tract.

The measurement of pancreatic function is even more difficult than that of hepatic function. The evidence to date should not be accepted as entirely conclusive of these contentions; however, the possibility of pancreatic involvement is one which should ever be kept in mind in the study of patients with hepatic disease.

Cholesterol and Cholesterol Esters of the Serum.—The value of the determination of cholesterol esters in the blood in cases of jaundice depends on the fact that, when taken in conjunction with the determination of the total cholesterol and bilirubin contents of the blood, it affords a method of distinguishing between jaundice due to biliary obstruction and that due to parenchymatous disease of the liver. Epstein [54] recently reported a comprehensive study of a large number of cases. In obstructive jaundice there is usually hypercholesteremia, which roughly parallels the degree of obstruction and bilirubinemia and returns to a normal level with the relief of the obstruction. The amount of cholesterol esters rises concomitantly with that of total cholesterol in about one-half the cases; in other cases (probably associated with greater damage to the liver) the value for cholesterol esters remains normal but lags relatively behind the increased content of free cholesterol. In cases of cholecystitis and cholelithiasis without obstruction, the blood cholesterol does not vary significantly.

In cases of degenerative diseases of the liver there is usually a marked divergence between the bilirubin and the cholesterol content of the blood. The more pronounced the damage to the liver, the greater the hypocholesteremia which accompanies the hyperbilirubinemia. In these cases the values of the cholesterol esters are even more depressed than that of the total cholesterol, and parallel the degree of hepatic

52. Michelazzi, A. M.: Action of Hydrochloric Acid on Glucemia of Hepatic Patients, Policlinico (sez. med.) **41**:78 (Feb.) 1934.

53. Foged, J.: Clinical Significance of Diastasuria: III. Diastasuria in Diseases of Biliary Tract, Hospitalstid. **75**:1359 (Nov. 24) 1932.

54. Epstein, E. Z.: Cholesterol of Blood Plasma in Hepatic and Biliary Diseases, Arch. Int. Med. **50**:203 (Aug.) 1932.

damage even more accurately. A rise in the value of the cholesterol esters in such a case may be the first indication of an improved prognosis. Similar experiments have been reported by Mjassnikow.[55]

Changes in the Serum Proteins.—The problem of the disturbance in the coagulation of the blood and the tendency to hemorrhage in jaundice is an old one. Various theories have been proposed to explain the abnormal mechanism of coagulation in obstructive jaundice, and each in turn has been largely abandoned. The calcium theory has not proved tenable, repeated analyses having shown that the total and the "available" serum calcium of jaundiced subjects usually fall within normal limits. Likewise, normal values have been obtained for blood platelets, for plasma fibrinogen, for fibrin and even for the clotting time of the blood. The explanation in vogue at present is the presence in the blood stream of a substance or substances which interfere with the process of coagulation. In support of this view is the fact that in many jaundiced patients the blood clot, although forming with normal rapidity, is large, friable and nonretractile, as though syneresis of the fibrin had been inhibited. In contrast to the normal compact clot, a porous mesh of this kind may permit the seepage of cells and plasma from a damaged blood vessel, and this may lead to the slow, persistent exsanguination encountered in cases of obstructive jaundice. The interfering substances, according to Barlik,[56] may be in the nature of antithrombin or antiprothrombin. These terms are concerned with the mode of action of the interfering material, but they tell nothing regarding its origin or chemical nature. Information bearing on this point is supplied by the recent investigation of Carr and Foote.[57] Bile is an excretory medium for a variety of substances which, as a result of biliary obstruction, may accumulate in the blood stream. Disturbances in the metabolic activity of the liver from the same cause also may lead to the accumulation in the blood stream of abnormal products of metabolism or to failure of the processes of removal or detoxification of toxic byproducts of the normal processes of metabolism.

An observation of Mueller and Sturgis[58] that cysteine inhibits coagulation of the blood induced Carr and Foote to study the possible

55. Mjassnikow, A. L.: Rôle of Liver in Cholesterol Metabolism, Klin. Wchnschr. **11**:1910 (Nov. 12) 1932.

56. Barlik, A.: Delayed Blood Coagulability in Obstructive Jaundice, Arch. f. klin. Chir. **176**:252 (Sept. 20) 1933.

57. Carr, J. L., and Foote, F. S.: Progressive Obstructive Jaundice: Changes in Certain Elements of the Blood and Their Relation to Coagulation, Arch. Surg. **29**:277 (Aug.) 1934.

58. Mueller, J. H., and Sturgis, S.: Prevention of Blood Coagulation by Cysteine, Science **75**:140 (Jan. 29) 1932.

relation of this amino-acid to the impaired clotting reaction in obstructive jaundice. Preliminary studies demonstrated that the addition of minute amounts of cysteine to normal blood shortened the coagulation time but changed the clot to a large, friable, nonretractile one, closely resembling that formed in the blood of jaundiced human subjects. The injection of large doses of cysteine into normal animals produced a similar effect. Color tests for cysteine demonstrated that none was present in normal plasma, whereas definite reactions were obtained on the plasma from jaundiced animals. Furthermore, the intensity of the test increased progressively with the tendency to hemorrhage.

The foregoing indications that cysteine, or perhaps a related mercaptan, is intimately related to the abnormal clotting reaction in jaundiced subjects prompted an investigation of the therapeutic action of brombenzene, a substance that combines with cysteine to form bromphenylmercapturic acid, which is excreted in the urine. The tendency toward bleeding was definitely reduced in the treated animals, and they did not die of hemorrhage. Crystals of bromphenylmercapturic acid were isolated from the urine.

This investigation, if confirmed, undoubtedly will constitute a valuable contribution to the current knowledge of the etiology of the hemorrhagic tendency in obstructive jaundice, but much more experimental work on the subject is needed before conclusions can be drawn. Likewise, although the beneficial action of brombenzene therapy is at least suggestive, it should be recalled that this substance is definitely toxic and should be used with the greatest caution. Perhaps of most immediate clinical import is the suggestion that an excess of protein, the metabolic precursor of cysteine and related mercaptans, should be avoided in the diet of patients with obstructive jaundice.

Whipple and his associates [59] showed that the liver is concerned with the formation of the various blood proteins. This is true not only of fibrinogen but perhaps of serum albumin and serum globulin as well. There is an increasing literature dealing with changes in the serum globulin. Most of this evidence, however, is indirect and was obtained by means of the sedimentation rate or by flocculation reactions.

No attempt will be made to review the sedimentation rate in relation to disease in general or the various factors which affect this test. Linton [60] considered an increase in the sedimentation rate the best index to the danger of postoperative hemorrhage in jaundiced patients. Clute

59. Holman, R. L.; Mahoney, E. B., and Whipple, G. H.: Blood Plasma Protein Regeneration Controlled by Diet: I. Liver and Casein as Potent Diet Factors, J. Exper. Med. **59**:251 (March) 1934.

60. Linton, R. R.: The Sedimentation Rate of Blood as an Index of the Haemorrhagic Tendency in Obstructive Jaundice, Ann. Surg. **91**:694 (May) 1930.

and Veal,[61] Burke and Weir [62] and Picardi,[63] on the other hand, expressed the belief that the results were too variable to make the test of prognostic value.

Disturbances in the quality of the serum proteins can also be shown by various precipitation tests. One of these, the Takata-Ara test, is made with a dilute solution of corrosive mercuric chloride. A positive result presumably indicates an increase in the globulin, particularly in the euglobulin fraction, of the serum, with a shift or an inversion of the albumin-globulin ratio, though Schindel [64] thought that the appearance of the lower forms of fatty acids in the serum may play a rôle in the production of a positive reaction. It is generally agreed [65] that while a negative reaction does not rule out hepatic disease, nevertheless a positive result is strongly indicative of the condition. The test is of particular value in cases of advanced parenchymatous damage, such as cirrhosis, in which the percentage of positive reactions varies from 68 (Rohrer [65a]) to 84 per cent (Schindel and Barth [65h]). In cases of other conditions such as fatty degeneration, syphilis, acute hepatitis or chronic passive congestion, a positive reaction may be given, though much less frequently. A negative reaction is the rule in uncomplicated cases of

61. Clute, H. M., and Veal, J. R.: The Prediction of Haemorrhage in Obstructive Jaundice by the Sedimentation Rate, Ann. Surg. **96**:385, 1932.

62. Burke, C. F., and Weir, J. F.: The Hemorrhagic Tendency in Jaundice: A Study of the Blood Fibrin, Sedimentation Rate, Coagulation Time, and Other Blood Factors, J. Lab. & Clin. Med. **18**:657 (April) 1933.

63. Picardi, G.: Erythrocyte Sedimentation Speed in Surgical Diseases of Biliary Tract, Policlinico (sez. prat.) **40**:1369 (Aug. 28) 1933.

64. Schindel, L.: Mechanism of Takata-Ara Test, Klin. Wchnschr. **13**:221 (Feb. 10) 1934.

65. (*a*) Rohrer, C.: Takata-Ara Reaction (Jezler Modification) in Diseases of Liver, Ztschr. f. klin. Med. **123**:637 (March 10) 1933. (*b*) Skouge, E.: Clinical Contribution to Latent Liver Diseases, Especially Latent Cirrhosis of Liver, Norsk mag. f. lægevidensk. **94**:393 (April) 1933. (*c*) Tannenholz, H.: Takata Serum Reaction as Diagnostic and Prognostic Aid in Syphilology and Dermatology, Am. J. Syph. **17**:352 (July) 1933. (*d*) Hugonot, G., and Sohier, R.: Takata-Ara Reaction: Test of Hepatic Insufficiency, Rev. méd.-chir. d. mal. du foie **9**:5 (Jan.-Feb.) 1934. (*e*) Lazzaro, G.: Reaction of Takata-Ara in Serum and Ascitic Fluid of Diseases of Liver, Policlinico (sez. med.) **41**:144 (March) 1934. (*f*) Crane, M. P.: A Modified Mercuric Chloride Reaction (Takata-Ara) in Cirrhosis and in Neoplasm of the Liver, Am. J. M. Sc. **187**:705 (May) 1934. (*g*) Jezler, A.: Clinical Experiences with Modified Takata Reaction, Klin. Wchnschr. **13**:1276 (Sept. 8) 1934. (*h*) Schindel, L., and Barth, E.: Significance of Takata Reaction for Diagnosis of Liver Diseases in Its Relation to Galactose and Bilirubin Tolerance Test, Klin. Wchnschr. **13**:1355 (Sept. 22) 1934. (*i*) Heath, C. W., and King, E. F.: The Takata-Ara Test in the Diagnosis of Liver Disease, New England J. Med. **211**:1077, 1934.

obstructive jaundice, carcinoma or, according to Neuweiler,[66] the toxicoses of pregnancy.

Seroreactions similar in character to the Takata-Ara reaction are those of Weltmann and Sieder[67] and the magnesium chloride test of Bauer.[68] In the former test 0.1 cc. of serum is added to each of a series of tubes containing 4 cc. each of solutions of various concentrations (from 0.1 to 0.01 per cent) of calcium chloride in distilled water. The serum is then coagulated by heating in a boiling water bath for fifteen minutes. Weltmann and Sieder[67] reported that the test is of value in the recognition of parenchymal injury to the liver, and this was confirmed by Massobrio and de Michelis[69] and by Pellegrini and Barsini.[70] The latter authors obtained positive reactions in cases of pernicious anemia, diabetes mellitus and chronic alcoholism, in which they thought that changes in hepatic function may occur.

The magnesium chloride test of Bauer is based on the addition of a 15.68 per cent solution of magnesium chloride to an equal volume of diluted serum. The solution is then heated on the water bath. Here, too, flocculation depends on an increase in the proportion of globulin in the serum. The majority of positive reactions were obtained in cases of hepatic cirrhosis or acute hepatic injury. Positive results were also the rule in cases of pernicious anemia. On the other hand, in cases of carcinoma, tuberculosis, syphilis and the like, negative reactions were the rule. Bauer considered this test of similar import to the Takata-Ara reaction but preferable because it is more sensitive and specific.

Phosphatase Content of the Blood Serum.—Enzymes which hydrolyze esters of phosphoric acid or phosphatases are observed in many mammalian tissues, including the liver. They are also present in the bile. Roberts[71] found the phosphatase content of the serum increased in a

66. Neuweiler, W.: Takata Reaction and Pregnancy Toxicosis, Klin. Wchnschr. **13**:1428 (Oct. 6) 1934.

67. Weltmann, O., and Sieder, B.: Significance of Weltmann's Coagulation Band for Diagnosis of Hepatic Disease, Wien. Arch. f. inn. Med. **24**:321 (Feb. 10) 1934.

68. Bauer, R.: Magnesium Chloride Test: New Reaction for Serum Proteins, Med. Klin. **30**:230 (Feb. 16) 1934.

69. Massobrio, E., and de Michelis, U.: Serum Coagulation of Weltmann in Hepatopathy in Relation to Protein Picture of Serum, Minerva med. **1**:147 (Feb. 3) 1934.

70. Pellegrini, M., and Barsini, G.: Behavior and Significance of Weltmann's Serum Reaction in Some Diseases: Research on Behavior of Electrolytic Threshold of Coagulo-flocculation to Heat of Exudates, Transudates and of Normal and Pathologic Cerebrospinal Fluid, Minerva med. **1**:154 (Feb. 3) 1934.

71. Roberts, W. M.: Variations in the Phosphatase Activity of the Blood in Disease, Brit. J. Exper. Path. **11**:90, 1930; Blood Phosphatase and the van den Bergh Reaction in the Differentiation of the Several Types of Jaundice, Brit. M. J. **1**:734, 1933.

series of cases of obstructive jaundice, whereas in cases of toxic, infectious or catarrhal jaundice the values were only slightly increased over the normal content. He therefore considered the test of value in differential diagnosis. Bodansky and Jaffe [72] and Armstrong, King and Harris [73] found that the serum phosphatase was markedly increased in experimental obstructive jaundice. However, Bodansky and Jaffe [74] also obtained high values in cases of hepatitis. Greene, Shattuck and Kaplowitz [75] reinvestigated the problem and found that phosphatase was present in samples of bile obtained from the gallbladder at operation or by duodenal intubation.

The phosphatase content of the serum was increased in cases of jaundice due to hepatitis or to obstruction of the biliary passages. This test was of no value in the differential diagnosis of the two conditions. The phosphatase content of the serum was not increased in cases of hemolytic jaundice, but was increased in cases of portal cirrhosis.

Miscellaneous Tests of Hepatic Function.—A multitude of tests designed to show changes in hepatic function have been described, and the number increases almost daily. De Flora [76] found that the ketone bodies in the blood of normal persons were increased for a period of from one to two hours after the ingestion of sugar. The level of the ketone bodies in the blood during fasting in patients with hepatic disease was higher than in normal persons, but it did not increase after the ingestion of sugar. Quick [77] reported that the synthesis of hippuric acid was diminished in patients with hepatic damage. It is also reduced in cases of nephritis, but Quick considered the test a valuable aid in the diagnosis of hepatic disease. Caccuri and Chiariello [78] injected amino-acetic acid intravenously and studied the changes in the amino-acid in

72. Bodansky, A., and Jaffe, H. L.: Increase of Serum Phosphatase After Bile Duct Ligation in Dog, Proc. Soc. Exper. Biol. & Med. **31**:1179 (June) 1934.

73. Armstrong, A. R.; King, E. J., and Harris, R. I.: Serum Phosphatase in Obstructive Jaundice, Canad. M. A. J. **31**:14 (July) 1934.

74. Bodansky, A., and Jaffe, H. L.: Phosphatase Studies: IV. Serum Phosphatase of Non-Osseous Origin: Significance of the Variations of Serum Phosphatase in Jaundice, Proc. Soc. Exper. Biol. & Med. **31**:107, 1933; Significance of Clinical and Experimental Serum Phosphatase Variations; Their Osseous and Non-Osseous Origins, J. Biol. Chem. **105**:xi, 1934.

75. Greene, C. H.; Shattuck, H. F., and Kaplowitz, L.: The Phosphatase Content of the Blood Serum in Jaundice, J. Clin. Investigation **13**:1079 (Nov.) 1934.

76. de Flora, G.: Ketonemic Curve After Ingestion of Sugar as Test of Hepatic Function, Riforma med. **12**:804 (May 24) 1934.

77. Quick, A. J.: Synthesis of Hippuric Acid: New Test of Liver Function, Am. J. M. Sc. **185**:630 (May) 1933.

78. Caccuri, S., and Chiariello, A.: New Procedure of Functional Examination of Liver: Deaminizing Power of Liver After Glyocoll Injection, Arch. d. mal. de l'app. digestif **24**:840 (Oct.) 1934.

the blood. A pathologic curve for the amino-acetic acid content of the blood and a delay in the removal from the blood stream of the injected amino-acid were reported in a series of patients with hepatic disease. Similar changes were observed in rabbits after the experimental administration of various hepatic poisons.

Monguió and Krause [79] found that the ammonia in the blood was increased in dogs with various types of hepatic injury. They considered that this was evidence of disturbance in the ureagenic function of the liver and that it furnished experimental evidence in support of the clinical use of high carbohydrate diets in diseases of the liver.

Nakagawa, Iimuro and Suzuki [80] injected 1.5 cc. of a 20 per cent solution of bile acid intravenously. Specimens of urine were then collected every thirty minutes for a two hour period. The reaction was considered positive if the urine showed a white turbidity following the addition of acetic acid, a positive Hay reaction and an increased content of urobilin or urobilinogen over that of the control. They believed that this is a sensitive test and that it shows functional impairment of slight degree. At the same time, it is of correspondingly less value for the differentiation of various types of hepatic lesions.

It has long been accepted that the clinical picture in the various types of jaundice is not always distinct. The same confusion is true of the pathologic changes, for many cases of chronic cholecystitis show accompanying hepatitis of varying degrees of severity. Infection may be absent in cases of biliary obstruction due to carcinoma of the head of the pancreas, but the resultant hydrohepatosis is responsible for parenchymal atrophy or the development of obstructive cirrhosis. The varieties of hepatogenous jaundice have been mentioned. When the different factors are taken into consideration it becomes obvious that the grouping of cases of jaundice into hepatic and obstructive types, as is done in clinical practice, is essentially arbitrary. It appears to us [81] that continuance of the search for functional tests which will distinguish specifically between the two groups of cases is not likely to be successful. The value of the present tests is not determined by the percentage of occurrence of positive results in cases of the hepatic and obstructive types of jaundice. Functional tests rather should be used in an attempt to determine the extent to which the various elements already referred to enter into the clinical picture.

---

79. Monguió, J., and Krause, F.: Significance of Ammonia Content of Blood for Estimation of Liver Function, Klin. Wchnschr. **13**:1142 (Aug. 11) 1934.

80. Nakagawa, S.; Iimuro, S., and Suzuki, S.: Bile Acid Tolerance Test for Determination of Hepatic Function, Klin. Wchnschr. **13**:1392 (Sept. 29) 1934.

81. Greene, C. H., and Shattuck, H. F.: The Clinical Use of Tests of Hepatic Function, Am. J. Digest. Dis. & Nutrition **1**:505 (Sept.) 1934.

FUNCTIONAL DISTURBANCES IN EXOPHTHALMIC GOITER AND PREGNANCY

Disturbances in hepatic function have been reported in a variety of diseases. The cause of the jaundice occasionally seen in patients with hyperthyroidism has been a subject of controversy. Schneider and Widmann,[82] Weller [83] and Beaver and Pemberton [84] have reported the occurrence of hepatic damage with degenerative changes, necrosis, subacute atrophy or moderate degrees of cirrhosis in patients with hyperthyroidism or exophthalmic goiter. Lichtman [85] also demonstrated that the oxidation of cinchophen is disturbed in such cases. He considered this test indicative of functional impairment, perhaps secondary to the depletion of glycogen in the cells of the liver.

The pathogenesis of eclampsia is by no means clear, but because pathologic changes are frequently noted in the liver there has been a great deal of interest in the results of functional tests during normal pregnancies and in patients with eclampsia. Hofbauer [86] and Soffer [87] found that the elimination of injected bilirubin was normal during the first half of the pregnancy but that there was a definite retention during the second half. Germer [88] studied the quinine-resistant lipase in the serum as an index of hepatic function. Positive reactions were the rule after the sixth or seventh month with a return toward normal levels just before delivery. The urobilinogen in the urine showed comparable changes. Huwer,[89] on the other hand, did not consider urobilinuria sufficiently marked to indicate impairment of the liver. Cantarow, Stuckert and Gartman [90] found normal values for the serum bilirubin. Retention of bromsulphalein was present in some but not

82. Schneider, E., and Widmann, E.: Clinical and Experimental Studies of Goiter Problem and of Exophthalmic Goiter, Deutsche Ztschr. f. Chir. **241**:15 (July 22) 1933.

83. Weller, C. V.: Hepatic Pathology in Exophthalmic Goiter, Ann. Int. Med. **7**:543 (Nov.) 1933.

84. Beaver, D. C., and Pemberton, J. deJ.: Pathologic Anatomy of Liver in Exophthalmic Goiter, Ann. Int. Med. **7**:687 (Dec.) 1933.

85. Lichtman, S. S.: Liver Function in Hyperthyroidism, Arch. Int. Med. **50**:721 (Nov.) 1932.

86. Hofbauer, J.: Hepatopathy of Pregnancy and Pathogenesis of Eclampsia, Zentralbl. f. Gynäk. **57**:35 (Jan. 7) 1933.

87. Soffer, L. J.: Bilirubin Excretion as Test for Liver Function During Normal Pregnancy, Bull. Johns Hopkins Hosp. **52**:365 (May) 1933.

88. Germer, K.: Comparative Investigations on Liver Function in Normal Pregnant Women, Ugesk. f. læger **95**:495 (April 27) 1933.

89. Huwer, G.: Blood Pigment Metabolism in Gestation: Function of Liver During Pregnancy, Ztschr. f. Geburtsh. u. Gynäk. **106**:324 (Oct. 13) 1933.

90. Cantarow, A.; Stuckert, H., and Gartman, E.: Studies of Hepatic Function: IV. Hepatic Function During Pregnancy, Am. J. Obst. & Gynec. **29**:36 (Jan.) 1935.

in all of the cases of eclampsia. They agreed with Dietel and Polak [91] that hepatic damage in eclampsia is more frequent than is indicated by the tests of hepatic function. Stander and Cadden [92] considered a rise in the uric acid content of the blood the best diagnostic criterion in preeclamptic states. They thought it evidence of hepatic disturbance, but the exact mechanism was not understood.

HEPATIC CIRRHOSIS

The present tendency is to divide cirrhotic processes in the liver into portal cirrhosis and obstructive biliary cirrhosis. In the past there have been many classifications of cases of portal cirrhosis into subgroups on an etiologic or a morphologic basis or on the basis of presumed differences in the clinical picture. The majority of such classifications have not been satisfactory, and the present tendency, as pointed out by Moon,[93] is to use the term "cirrhosis" as synonymous with "chronic diffuse hepatitis." Any agent or combination of agents which produces chronic diffuse hepatic inflammation results in some degree of cirrhosis. The degree and character of the cirrhosis may vary, but the essential features of the cirrhotic process are (1) degeneration and destruction of liver cells, (2) regeneration of hepatic cells from those which escaped destruction and (3) proliferation of connective tissue.

Moon, who reviewed the literature on experimental cirrhosis in an attempt to evaluate the bearing of these experiments on cirrhosis in man, pointed out that numerous agents, diverse in character, are capable of causing degeneration and necrosis of hepatic cells. These agents include various chemicals, both organic and inorganic, certain drugs and tarlike substances, foreign proteins and products of protein decomposition, bacterial products, immune serums and infections. The continued or repeated action of these agents has resulted in the production of chronic diffuse hepatitis, as indicated by degeneration and necrosis, regeneration of parenchyma and proliferation of fibrous tissue.

Probably the majority of these agents have no etiologic significance in the development of cirrhosis in man. Yet the results of the investigation of their action have contributed greatly to an understanding of the mechanism by which cirrhosis develops. In every instance in which the prolonged action of an agent has resulted in a degree of cirrhosis,

91. Dietel, F. G., and Polak, A.: Late Disturbances of Functions of Liver and Reticulo-Endothelial System After Eclampsia, Arch. f. Gynäk. **152**:469 (Feb. 22) 1933.

92. Stander, H. J., and Cadden, J. F.: Acute Yellow Atrophy of the Liver in Pregnancy, Am. J. Obst. & Gynec. **28**:61 (July) 1934; Blood Chemistry in Pre-Eclampsia and Eclampsia, ibid. **28**:856 (Dec.) 1934.

93. Moon, V. H.: Experimental Cirrhosis in Relation to Human Cirrhosis, Arch. Path. **18**:380 (Sept.) 1934.

the acute effects have been degeneration and necrosis of hepatic cells. Cirrhosis, like other chronic inflammations, results from parenchymatous injury followed by repair. If such injury is severe, continued or repeated, repair will be accompanied by fibrosis. This evidence should tend to allay a controversy of long duration between certain groups of European pathologists.

A few agents which have met satisfactorily the rigid criteria for the production of Laënnec's cirrhosis are phosphorus and alcohol, manganese chloride with phenylhydrazine, carbon tetrachloride, tars, bacterial infections and combinations of infection and other agents. Each of these agents has produced distortion of the architecture of the organ, in which marked alteration of the lobular pattern was evident. The islands of regenerated hepatic cells occurred as nodules rather than as lobules and indicated the type of circulatory disarrangement which is characteristic of Laënnec's cirrhosis. In experiments with carbon tetrachloride, the circulatory disturbances resulted in portal circulatory obstruction, as indicated by ascites and by the development of collateral venous channels.

The belief that cirrhosis is caused by alcohol has not received experimental support. Without exception, the agents which have produced cirrhosis experimentally have caused hepatic necrosis. Alcohol, even in large amounts and with long-continued use, has caused only parenchymatous degeneration and fatty changes. These changes have resulted neither in necrosis nor in permanent hepatic changes. However, the probability that alcohol acts as a contributing or predisposing factor has received experimental support. Alcohol has been found to accentuate the injurious effects of bacteria, phosphorus, chloroform and carbon tetrachloride on the liver of animals. It is probable that alcohol may similarly accentuate the effects of injurious agents on the human liver. By virtue of this property, alcohol may be an important contributory factor in the development of human cirrhosis.

Cirrhosis resulting from treatment with tar has duplicated Laënnec's cirrhosis with remarkable accuracy. The gross and microscopic characteristics have fulfilled the rigid requirements. The splenic changes have resembled those accompanying Laënnec's cirrhosis, and ascites has been an almost constant associated feature. The fact that the experiments were made on rabbits makes a high degree of conservatism necessary in their interpretation. However, the high percentage of positive results makes it probable that coccidiosis was not concerned. In some experiments, erroneous conclusions were partially obviated by examinations of the liver prior to experimentation.

The injurious effects of hydrazine and similar organic chemicals and the production of cirrhosis by means of tars have perhaps a deeper sig-

nificance than is apparent. Many investigators have expressed the belief that various substances present incidentally in alcoholic liquors may be responsible for the cirrhosis occurring among drinkers of these beverages. Many such contaminants have been investigated without significant results. The tarlike products or substances of the benzene series formed by the charring of casks used for the aging of liquor have not been investigated. Liquors aged in charred casks contain visible quantities of a brownish substance dissolved from the semicharred wood. Such substances might produce effects similar to those of tars. Is it possible that such substances may be responsible for the development of cirrhosis in habitual drinkers of alcoholic liquors?

There is evidence that metabolic disturbances may be important contributing factors. Medical literature contains records of many observations on the simultaneous occurrence of exophthalmic goiter and cirrhosis. A survey of the occurrence of cirrhosis in different sections of the United States showed a suggestive relationship between cirrhosis and disease of the thyroid gland. The states having the highest death rate from disease of the thyroid had also the highest death rate from cirrhosis. A similar relationship is exemplified in European countries. The highest incidence of cirrhosis on record is in Switzerland, where goiter also is most prevalent. Livers with low glycogen content have an increased susceptibility to injury. Hyperthyroidism may contribute to the development of cirrhosis by producing hepatic glycopenia. Marked thyrotoxicosis produces extensive hepatic necrosis. Hence thyrotoxicosis may be a direct cause of cirrhosis.

Infections in animals are known to cause hepatitis which closely resembles Laënnec's cirrhosis. The high incidence of cirrhosis in tropical countries, associated with infectious diseases peculiar to those regions, is significant. It is admitted that congenital syphilis may result in a form of cirrhosis resembling that bearing the name of Laënnec. Many observers have demonstrated a relationship between streptococcic infection and cirrhosis. It is probable that chronic diffuse infections of the liver are important factors in the etiology of cirrhosis.

It is significant that combinations of agents have been found more effective in the production of cirrhosis than any of the agents alone. The combination of alcohol with phosphorus, of manganese chloride with colon bacilli or with hydrazine, of chloroform with alcohol, cholesterol, streptococci or colon bacilli, and of alcohol with bacteria or with carbon tetrachloride and the effect of diet in experiments with phosphorus, chloroform and carbon tetrachloride are important examples. The results in such instances suggest the importance of combinations of agents in the etiology of cirrhosis in man.

A survey of experimental and clinical studies on cirrhosis convinces one that no single causative factor is responsible. Cirrhosis is synon-

ymous with chronic progressive hepatitis. Its etiology will be found to be as variable as are the agents which, singly or in combination, may cause chronic diffuse progressive inflammation of the liver.

While Moon was concerned primarily with the study of experimental forms of cirrhosis, the view is in accord with those of Althausen [94] and of Menne and Johnston,[95] who were interested in the clinical features of the condition.

Various clinical reports have presented cases which further stress the similarity between the clinical and experimental forms of cirrhosis. The report of Yenikomshian [96] is of interest in emphasizing the frequency of cirrhosis in a population in which the use of alcohol is tabu. He expressed the belief that chronic infection, produced by chronic malaria or amebic dysentery or by a combination of the two, is primarily responsible for the frequency of cirrhosis in Syria and Lebanon. Poindexter and Greene [97] reported a case of portal cirrhosis which was due to long continued exposure to the fumes of carbon tetrachloride and could be considered the clinical counterpart of the cirrhosis experimentally produced in animals by the action of this substance. The rôle of cinchophen and of cinchophen derivatives in producing toxic hepatitis or subsequently hepatic cirrhosis has been brought to the attention of clinicians during the past few years. The literature on this subject has been reviewed by Weir and Comfort [98] and by Bloch and Rosenberg.[99]

McCartney [100] reviewed the observations in a series of 245 cases of portal cirrhosis detected in routine postmortem examinations. There was an incidence of 2.05 per cent, which agreed well with that of 1.36 per cent reported by Menne and Johnson. The weight of the liver was much more variable than in normal persons, though there was a disproportionately large number of hypertrophic livers occurring in the earlier decades of adult life and of atrophic livers in persons in the later

94. Althausen, T. L.: Etiology and Pathogenesis of Hepatic Cirrhosis, Ann. Int. Med. **6**:1080 (Feb.) 1933.

95. Menne, F. R., and Johnston, T. W.: Cirrhosis of Liver: Its Character and Incidence in Six Thousand Five Hundred Autopsies, Northwest Med. **32**:129 (April) 1933.

96. Yenikomshian, H. A.: Nonalcoholic Cirrhosis of the Liver in Lebanon and Syria, J. A. M. A. **103**:660 (Sept. 1) 1934.

97. Poindexter, C. A., and Greene, C. H.: Toxic Cirrhosis of the Liver: Report of a Case Due to Long Continued Exposure to Carbon Tetrachloride, J. A. M. A. **102**:2015 (June 16) 1934.

98. Weir, J. F., and Comfort, M. W.: Toxic Cirrhosis Caused by Cinchophen, Arch. Int. Med. **52**:685 (Nov.) 1933.

99. Bloch, L., and Rosenberg, D. H.: Cinchophen Poisoning: A Report of Seven Cases with Special Reference to a Rare Instance Complicated by Multiple Gastric Ulcers, Am. J. Digest. Dis. & Nutrition **1**:433 (Sept.) 1934.

100. McCartney, J. S.: Latent Portal Cirrhosis of the Liver, Arch. Path. **16**:817 (Dec.) 1933.

decades. Livers which showed the more advanced degrees of cirrhosis tended to be smaller than those in which the process was less advanced.

Hijmans, van den Bergh and Kamerlin[101] and Fellinger and Klima,[102] among others, emphasized the tendency to anemia in portal cirrhosis. This anemia, which is typical of the advanced cases of cirrhosis, is macrocytic in type with an increased color index and morphologic changes in the blood cells resembling those seen in pernicious anemia. The authors therefore expressed the belief that a hepatic element may be present in pernicious anemia, and they discussed at length the possible interrelationship of cirrhosis and anemia.

The treatment of cirrhosis has undergone little change during the period under consideration. The elimination of the causative agent when it can be identified, diets high in carbohydrate and low in salt or with an acid ash and the use of ammonium or potassium salts frequently in combination with mercurial diuretics, such as salyrgan, are the measures most in favor. McCabe and Hart,[103] among others, advocated the use of large doses of insulin in addition, but the good results which they reported could be ascribed equally to the use of a carbohydrate diet. Certainly the majority of patients with hepatic cirrhosis, with the exception of those with hemochromatosis, show no clinical signs suggesting the presence of diabetes or a failure in the supply of insulin. McCartney reported that in 35 per cent of the cases which he studied the cirrhosis was latent and had not been recognized chemically. Perhaps the most important factor in the management of cirrhosis, as stressed by Althausen and by Chapman, Snell and Rowntree,[104] is its early recognition and treatment before the development of ascites or the production of irreparable hepatic damage.

HEPATOSPLENOGRAPHY

When a colloidal solution of thorium dioxide is injected intravenously, the particles of thorium dioxide which are opaque to the roentgen rays are phagocytosed by the histiocytic cells of the reticulo-endothelial system. The roentgenographic demonstration of structural changes in

101. van den Bergh, A. A.; Hijmans and Kamerling, A. W. C. G.: Cirrhosis of Liver with Hemolytic Anemia and Severe Hematinemia, Nederl. tijdschr. v. geneesk. **78**:4432 (Sept. 29) 1934.

102. Fellinger, K., and Klima, R.: Studies on Anemias in Cirrhosis of Liver, Wien. klin. Wchnschr. **46**:1191 (Oct. 6) 1933.

103. McCabe, J., and Hart, J. F.: Treatment of Hepatic Cirrhosis with Insulin: Preliminary Report with Case Histories, New York State J. Med. **33**:1924 (Aug. 1) 1933.

104. Chapman, C. B.; Snell, A. M., and Rowntree, N.: Compensated Cirrhosis of the Liver: A Plea for More Intensive Consideration of the Earlier Stages of Disease of the Hepatic Parenchyma, J. A. M. A. **100**:1735 (June 3) 1933.

the liver and spleen is thereby made possible. The extensive literature on this technic has been extended during the past two years by the reports of Reeves and Apple,[105] Ericksen and Rigler [106] and Yater and Otell.[107] The last two reports of Yater and Otell [107b] dealt with series of 82 and 100 cases, respectively. All these authors were in agreement that the method is of value in detecting the nature of a mass in the upper part of the abdomen, in the preoperative recognition of hepatic metastases in cases in which an operation for cancer, particularly of the gastro-intestinal tract, is contemplated, in the diagnosis of hepatic disease and in the recognition of such conditions as cirrhosis, gumma, abscess, cyst or primary tumor of the liver.

Ericksen and Rigler and Yater and Otell called attention to the report of the Council on Pharmacy and Chemistry of the American Medical Association [108] and urged caution in the intravenous use of thorium dioxide because it is a heavy metal and insoluble after being phagocytosed by the reticulo-endothelial cells and because its excretion is slow and probably requires years to be completed, if it ever is. Thorium is radioactive, and while the total dose of alpha rays is slight (equivalent to from 1.5 to 3 micrograms of radium) and no immediate harmful effects, either local or general, have been observed, the possibility of remote effects cannot be excluded. Shute and Davis,[109] in addition, reported that in rabbits and dogs large doses of thorium dioxide produced temporary degenerative changes in both the liver and the spleen. While the doses of thorium dioxide used in clinical practice are well within the apparent limit of safety of this procedure, it is probably wisest for the present to follow the suggestion of Yater and Otell and employ hepatosplenography only on the patients who are subjects of a rapidly fatal disease.

---

105. Reeves, R. J., and Apple, E. D.: The Use of Thorium Dioxide in the Diagnosis of Liver Abscess, J. A. M. A. **100**:1682 (May 27) 1933.

106. Ericksen, L. G., and Rigler, L. G.: Roentgen Visualization of Liver and Spleen with Thorium Dioxide Sol, with Particular Reference to the Preoperative Diagnosis of Carcinomatous Metastases to the Liver, J. A. M. A. **100**:1758 (June 3) 1933.

107. (*a*) Yater, W. M.: Diagnosis of Diseases of Liver, with Especial Reference to Thorotrast Hepatosplenography, M. Ann. District of Columbia **2**:156 (July) 1933. (*b*) Yater, W. M., and Otell, L. S.: Differential Diagnosis of Diseases of Liver and Spleen with Aid of Roentgenography After Intravenous Injection of Thorium Dioxide Sol (Thorotrast): Experience with Eighty Patients, Ann. Int. Med. **7**:381, 1933; Hepatosplenography with Thorium Dioxide Sol: Clinical Experience with One Hundred Patients, J. A. M. A. **101**:507 (Aug. 12) 1933.

108. Thorotrast, Report of Council on Pharmacy and Chemistry, J. A. M. A. **99**:2183 (Dec. 24) 1932.

109. Shute, E., and Davis, M. E.: Histologic Changes in Rabbits and Dogs Following Intravenous Injection of Thorium Preparations, Arch. Path. **15**:27 (Jan.) 1933.

News and Comment

AMERICAN HEART ASSOCIATION, INC.

The Eleventh Scientific Session of the American Heart Association will be held on Tuesday, June 11, 1935, at the Hotel Claridge, Atlantic City, N. J. The program will be devoted to various phases of cardiovascular disease.

COMING MEETINGS

The American Society for Clinical Investigation will meet on May 6 at the Hotel Chalfonte-Haddon Hall, Atlantic City.

The Association of American Physicians will meet at the Hotel Chalfonte-Haddon Hall, Atlantic City, on May 7 and 8.

METHODIC CAMPAIGN AGAINST RHEUMATISM

The Ligue Internationale contre le Rhumatisme will hold its fifth congress at Lund, Sweden, in September 1936.

Dr. S. Ingvar, professor of internal medicine at Lund, is chairman, and Prof. Dr. G. Kahlmeter of Stockholm is secretary.

Book Reviews

A Manual of the Practice of Medicine. By A. A. Stevens, M.D. Thirteenth edition. Price, $3.50. Pp. 685. Philadelphia: W. B. Saunders Company, 1934.

In 1892, Dr. Stevens, then an instructor in physical diagnosis in the University of Pennsylvania, published the first edition of this manual. It was written at the request of many students, with the hope that it would serve as an outline of the practice of medicine "which shall be enlarged upon by diligent attention upon lectures and critical observations at the bedside." It proved a successful venture, for the fourth edition appeared in 1896. This edition was reviewed in *The Journal of the American Medical Association* (**28**:664 [April 3] 1897). The reviewer commented: "This little manual has reached its fourth edition—evidence of merit. Its author understands the art of constructing a clear and fairly comprehensive abstract of the contents of the larger works of medicine, to which due reference is made in the preface. The result is a convenient pocket companion that will be found useful by the student who is preparing a cram for examination, or even by the newly fledged professor who is about to step forth into the arena. But for students who are engaged in class-work such hand-books are too sketchy, and, consequently, dry and uninteresting—mere skeletons, devoid of attraction."

The life history of the book is of some interest: During its first ten years of existence six editions were necessary, during its second ten years four editions and during its third ten years three editions. These figures suggest, perhaps, that with the passage of time and the changing trends in medical education students no longer cram for examinations as they did, newly fledged professors are less diffident about stepping forth into the arena than they were, and there is less demand for this kind of a compendium.

However, this thirteenth edition, like its predecessors, appears as a well articulated volume. It is deliberately sketchy but very much up to date, containing short summaries regarding subjects which have come to the foreground since 1928, such as agranulocytic angina, hyperparathyroidism, psittacosis and spontaneous subarachnoid hemorrhage. No doubt a manual of this sort has a function; what was said of the fourth edition in 1897 describes adequately the thirteenth edition of 1934.

The Laboratory Notebook Method in Teaching Physical Diagnosis and Clinical History Recording. By Logan Clendenning. Price, 50 cents. Pp. 71. St. Louis: C. V. Mosby Company, 1934.

In essence this is a notebook with headings dealing with the various points in physical diagnosis which the student can fill out as he examines the patient. The object is to fix in the mind of the student what he actually sees, learns and feels by making an accurate record. The idea seems a good one.

The Spastic Child. By Marguerite K. Fischel. Price, $1.50. Pp. 97. St. Louis: C. V. Mosby Company, 1934.

This book is a record of rehabilitation—"successfully achieved muscle control"—of patients with Little's disease, written from a somewhat sentimental point of view.